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FESTSCHRIFT

in Honor of

DR. EDWARDS A. PARK

The JOURNAL OF PEDIATRICS

Vol. 41 December, 1952 No. 6

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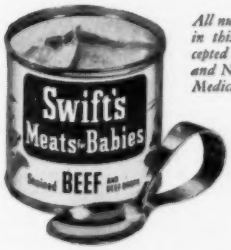

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Dr. Edwards A. Park

FESTSCHRIFT

in Honor of

DR. EDWARDS A. PARK

on the occasion of his Seventy-Fifth Birthday,

December 28, 1952

THE JOURNAL OF PEDIATRICS

Vol. 41 December, 1952 No. 6

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FOREWORD

THE JOURNAL is very happy to present this issue in the form of a Festschrift in honor of Dr. Edwards A. Park on the occasion of his 75th birthday, December 28, 1952.

In his long and active career, Dr. Park has earned for himself a well-deserved niche in the "Hall of Fame" among the great names in pediatrics. Not only have his individual contributions in the field of research added immeasurably to our knowledge, but he has had that rare gift of inspiring many who have come under his influence to attain distinction in their own right as leaders in research and pedagogy. The contributions to the Festschrift are by these former students and associates. The Editorial Board wishes to express its thanks to the two "Guest Editors," Dr. Francis F. Schwentker and Dr. Lawson Wilkins of the Hopkins pediatric clinic. Their assistance in the selection of contributors was invaluable. The JOURNAL regrets that the limitation of pages available for the issue prevented the inclusion of the many others of Dr. Park's associates who by their work and position deserved to be asked to contribute.

Among the many positions which Dr. Park has held was membership for several years on the Editorial Board of the JOURNAL, where he developed and edited the department, "The Social Aspects of Medicine." Its purpose was a forum for the pro and con discussion of the controversial social and economic problems confronting medicine. It was not a department for the expression of Dr. Park's personal viewpoints, but reflected his broad-mindedness and sense of fair play. Would that pediatrics and medicine had more men with the intellectual integrity, the sense of professional and social responsibility, the rectitude, and the courage to stand openly for their beliefs. It is these qualities, which are so fundamental in Dr. Park's character, as well as his scientific accomplishments, that have endeared him to his associates and have won the respect and admiration of the entire medical profession.

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DR. PARK AS A TEACHER

FRANCIS F. SCHWENTKER, M.D.
BALTIMORE, MD.

THE characteristics which make a man an outstanding teacher are so complex and interwoven that any analysis of them is almost futile. Certainly all who know Dr. Park consider him an outstanding teacher. And yet he has never been a teacher in the ordinary sense. He dislikes the formal lectures and clinics which are required for undergraduate students. He is more nearly a teacher in the sense of the older philosophers who gathered about them a group of students who learned, not through formal teaching, but by the comprehensive discussions in which all participated.

We were never his students—we were always, in his eyes, colleagues, and in our eyes, disciples. His influence has not been as much that of a teacher; it has been that of a leader. It is true we have learned from his great fund of medical information. Yet all of this is insignificant compared to the total influence he has had on our lives. This extended far beyond the pediatric field. We learned sound medical judgment; a respect for reasonable scientific analysis; a disdain of sloppy, inaccurate thinking; the value of and interest in subjects beyond the medical field; the futility of pomp and ceremony; the joy of humility; the reward of hard work, and the satisfaction of service for the sake of service.

These things we learned through his teaching. Yet it is not clear whether Dr. Park ever had a plan of teaching. Those who are dedicated to a principle need no plan. Dr. Park's principles are simple. He believes that no man advances except by study and observation. He considered everyone in his department, including himself, as a student. On the other hand, he looked to everyone as a teacher. The "greenest" intern was encouraged to tell what he knew. This was what made his noon staff conferences so profitable. Every shred of information on the subject was gathered from every individual who attended. No one was student; no one was teacher.

In these conferences he often took a back seat, usually physically, and always figuratively. Yet he watched over the progress of each conference carefully. If the flow of information was unsatisfactory he might interpose some from his enormous memory or more usually he would ask a question of some member of the group which would elicit the pertinent information and set the course of the discussion back into profitable channels. Frequently the questions he asked were ones for which he already had the answer. Otherwise how could they be so close to the point? He preferred to stimulate discussion rather than dole out information.

More than one visitor from other clinics, impressed by Dr. Park's reputation as a clinician and teacher, has left one of his noon conferences with a feeling of disillusionment. More

than one has said to me in effect, "I expected to find a great teacher. Yet he answered no questions and those he asked were ones I would have expected from a young man of less experience." But if these same men were asked had they learned from the conference, the answer was always affirmative. One has to know Dr. Park to know his methods.

He has always disliked leaving a question with an unsatisfactory answer. It was not unusual when a question could not be answered during rounds on the ward for him to go to the telephone and call Dr. Ford or Dr. Dandy or anyone he thought might have the answer and put the question to him. I have several times asked him a casual question in his office which he was unable to answer to his own satisfaction. "But Dr. X will know," he said and immediately put in a long distance call to Dr. X. In such circumstances time meant nothing to him. It was most important to get the best possible answer to the question before the matter was dropped. All of his residents have, on such occasions, despaired of getting a noon conference ended in time to keep up to the daily schedule.

His own interest in learning along with his students is almost an obsession. It was always a point of great amusement to his staff when a visitor arrived to learn about the methods of pediatric care at the Harriet Lane Home. It mattered not whether the individual was a fledgling pediatrician or a professor from some other school. The discussion was always so managed by Dr. Park that when the visitor left, Dr. Park had extracted all he knew concerning the subject under discussion. The visitor may or may not have learned much but he departed glowing in his sense of importance.

I do not believe this gentle "pumping" of visitors was a method of learning of which Dr. Park himself was conscious. It stemmed from his own sense of humility and his high regard for the feelings of others. Humility associated with ability and achievement is rare. In Dr. Park it has often been present almost to an extreme. A colleague once found him sitting in the last row of chairs at a pediatric meeting. "Why don't you sit up front and engage in the discussion?" he asked. The reply was, "It is better to be discovered than found out."

He has never lost an opportunity to elevate the position or esteem of one of his subordinates. I remember making rounds with him on the private floor while I was an intern as green as the next. The mother of a patient with leukemia had a barrage of questions she wanted answered. Each one was referred to me and if I fumbled in the answer, his general reply was, "Now, Dr. S. knows much more about this than I do but if we asked him, I'm sure he would say . . ."

As I have said, it is doubtful whether Dr. Park ever constructed a detailed plan of teaching. Yet a plan evolved, fashioned on the basic ideas which were his principles. From them many important changes came about. The noon conferences were thrown open to and were popular with practicing pediatricians. The residency system was strengthened, under which all children in the wards were the patients of the resident who was responsible only to the professor. An extensive social service program was

inaugurated to make sure that the temporary advantages of Harriet Lane were made permanent in the home. Other departments were lured into the pediatric circle, not as consultants but as collaborators. The children's psychiatric service was begun; otolaryngologists, orthopedists, and dermatologists began functioning in the Harriet Lane outpatient department. Special clinics were inaugurated so that the patients would receive expert care but more important so that the information obtained would be worked out and presented. He himself began the chest clinic; he inspired Dr. Taussig to develop the cardiac clinic; he started Dr. Wilkins, and later Dr. Bridge and Dr. Kajdi, in work on epilepsy. Later he encouraged Dr. Wilkins in the potential opportunity in endocrinology. He guided Dr. Holt into the field of fat metabolism.

These were advancements within his own department. But his influence and guidance beyond that area are also substantial. He saw the opportunities in infectious diseases at Sydenham Hospital and persuaded the Commissioner of Health to place that institution under good medical and scientific leadership. He was instrumental in establishing the pediatric department at City Hospitals on a full-time basis and recommended the man who has made it an outstanding service.

Early in his career he began a collection of "Medical Notes." They were abstracts of unusual cases or of lectures or correspondence on some subject. Soon after his coming to Harriet Lane, they assumed such a volume that the entire resident staff was enlisted to keep them current. From this has come a collection of notes of tremendous importance, one frequently consulted about unusual cases or by authors struggling with a new textbook. Along this same line he began a collection of photographs of unusual cases called the "Album." This too grew to tremendous proportions and is a constant source of information to many.

In his own work he is meticulous and honest to an extreme; he expects the same honesty and exactitude from his associates. He never asks for it—he expects it. The intern who failed in this respect never saw a second year at Harriet Lane. This even went as far as handwriting. A history written in an illegible fashion was as unacceptable to him as a physical examination only half done. He himself felt a great sense of responsibility to his patients. He took infinite care to see that everything was done. Once a patient was his responsibility, he never forgot the fact. When I was resident he often called me late at night to tell me he had been thinking about some patient I had asked him to see during the day and had some further suggestions to make.

When he retired I asked him to take an active part in teaching and to make rounds on the wards for the benefit of the house staff. "I just can't do it," he said, "I'm really a biologist now. If I were to take clinical responsibilities, I would have to keep abreast of the current pediatric literature and just don't have the time. It wouldn't be fair to the resident staff." It was impossible to convince him he could forget the current literature for ten years and still be ahead of the rest of us.

Mention has already been made of his ability to see potential opportuni-

ties in new fields. It was because of this that he was able to guide so many of his students into successful careers in different areas of medical knowledge. He has always been on the alert for new ideas. When one came to him he presented it to a colleague or junior member of his department. He played a major role in the initiation of the work which led to the development of the operative measures for the relief of the tetralogy of Fallot. In 1934 he stopped me in the corridor and asked whether some bacteria did not suppress the growth of others in culture media. When I agreed he asked whether it might not be possible to study this phenomenon with an idea of extracting the active principle to use in the treatment of infections. I thought this was just a "brainstorm" and did nothing. It took a few more years and the accidental discovery of penicillin to prove how close his thinking had been to a great new principle and how miserably I had failed to recognize it.

Out of the raw material which filtered into the Harriet Lane staff year by year he molded, without apparent effort, a group of pediatricians who have stood high in both academic and practicing ranks. Without knowing all of his students, I count seventeen who now head departments of pediatries in teaching hospitals or hold equivalent positions. In every man who became a member of the Harriet Lane staff there developed a loyalty to Dr. Park and the institution seldom seen in other areas. This loyalty is born of a sense of respect, love, and devotion to "The Professor," professionally and personally. It has been nourished by the gratitude of all of his students for the influence of his principles and character on their lives. Even if we were to overlook the great benefits Dr. Park has given personally in the clinical field to his many patients; even if we were to forget the significant advances his investigations have made in the scientific field; if we were to consider only the benefit to the world of his abilities as a teacher and leader of men, we are unanimous that Dr. Park is a great man, whose humble devotion to service is leaving a lasting imprint on the world.

PRESENTATION OF THE KOBER MEDAL TO DR. EDWARDS A. PARK

JAMES L. GAMBLE, M.D.
BROOKLINE, MASS.

I AM grateful to President Dochez for the privilege of presenting the Kober medal to my friend and colleague over many years. At the outset of this pleasant assignment I find a bothersome obstacle; the modesty of the recipient is so immoderate that he dislikes laudation. However, this can't be quite the case. So I shall praise him all that I dare to but I will watch him closely and if the right hand corner of his mouth turns downward I shall retreat but if it goes upward I shall advance.

When Dr. Park graduated from Yale with the class of 1900 he made up his mind to study medicine. It was not an easy decision. His forbears were theologians in unbroken line all the way back to Jonathan Edwards, which is why we call him Ned. So that the choice of medicine for his career required the courage to disobey a fundamental tenet of Calvinism, predestination. His apostasy should not, I would say, be regarded as a mutation but rather as an adaptation, in the wide field of humanitarian endeavor. Theology is, I suppose, an intellectual and philosophical pursuit devoted to betterment of human behaviour. So the step to the mission of medicine is a short one.

Following his medical student years at the College of Physicians and Surgeons he served a year of interneship at the Roosevelt Hospital and six months as resident physician at the New York Foundling Hospital, and it was there that he met John Howland, who was an attending physician. He returned to the College of Physicians and Surgeons as an instructor in medicine and pediatrics. He also held the Proudfit Fellowship in Medical Research and, for a time, an instructorship in pathology. Of much more import to his young career than these high offices was the warm friendliness of the Bard Professor of Medicine, Theodore Janeway. To his delight he was permitted to share in Dr. Janeway's early studies on blood pressure which upset the current concept that epinephrin was in command. This was his first taste of research and he did not greatly mind that it cost him one of his lucrative instructorships when Dr. MacCallum fired him for flagrant absenteeism.

Meantime pediatrics was gathering momentum in Baltimore. John Howland had been appointed Von Pirquet's successor and was beginning to build a department which was to carry pediatrics very rapidly forward. In the year 1912, he asked Dr. Park to join in this enterprise. Dr. Janeway sensed the size of the opportunity and generously insisted that Dr. Park must accept it.

Before going to Baltimore he spent a year in Germany in the laboratory of an eminent pathologist, M. B. Schmidt, at Marburg. With an eye cocked at rickets, he learned the marvels of the processes of bone growth, the manner of their disruption by dis-

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ease and discovered an enduring delight in this wide field of study. To complete this paragraph crescendo, he also discovered in Marburg an attractive young lady from England and this time he did not oppose predestination.

My friendship with Dr. Park began in 1915 when I went to Baltimore to join the group of young pediatricians who were gathering about Dr. Howland, attracted by the rumor of opportunity to study disease in the clinic by appropriate methodology borrowed from the fundamental sciences. We found laboratory equipment far beyond anything that had yet been given to a clinical department in this country. The Harriet Lane was new and shining and contained in glorious abundance, from the young investigator's point of view, diseases which openly invited study by the methods at hand. We took the cream gaily from the top of the bottle and none of us, I am sure, ever had such happy years again.

Dr. Park was ready for rickets, which at that time was the largest disease of infancy. Very few infants in urban communities escaped at least a touch of rickets. This need not have been so. That cod liver oil will cure rickets had been discovered some two hundred years before and for generations students of rickets had been convinced of the rickets preventive effect of sunlight. But at the turn of the century medicine became devoutly scientific and the notion that oil from the liver of a codfish could cure a human ailment received the disrespect it so obviously deserved even in Massachusetts. When I was a student we were told this quaint bit of therapeutic lore and we were very amused. So it was evident that if this chief scourge of infants since the time that man invented clothing and shelter was ever to be removed, this would have to be done in scientifically acceptable fashion.

This came to pass with remarkable rapidity following the discovery by Mellanby in England that rickets could be produced in animals by defective diets. This new experimental approach led at once to intensive study of the pathogenesis of rickets by many investigators with the splendid result that within a few years rickets became a preventable disease, except for a small abstruse remnant which is not due to a simple dietary defect.

The Baltimore team of Macollum, Simmonds, Park and Shipley made a very large contribution to this achievement of the ultimate against a disease. A series of experiments culminated in 1923 in the discovery of Vitamin D. These experiments also gave a remarkably complete account of the relation of alterations of calcium and of phosphorus intake, along with lack of D, to various types of disturbance of bone growth and calcification. From his position at the microscope Dr. Park provided expert guidance of these experiments, which altogether deserve the lofty adjective, classical. Rickets would have been demolished without assistance from Dr. Park but not with the elegance of ceremonial which this grand old disease deserved and which his knowledge of the histopathology of bone provided.

Although Dr. Park assailed rickets with the same earnest anger that his forbears used against the devil, and with far more success, he could be a compassionate investigator. At that time the thymus gland stood accused of unphysiological activities alleged to

be dangerously subversive of the steady state. It was whispered that the thymus was the leader of a conspiracy vaguely described as Status Thymicolymphaticus with the malign intent of causing sudden and violent death of infants. Dr. Park was outraged by the inadequacy of the evidence and came to the defense of this gentle gland. In an extended series of extirpation experiments, Park and McClure established the innocence of the thymus, on the somewhat inglorious premise of physiological impotence. This verdict was a severe blow to witch hunting endocrinologists but it gave great comfort to a badly frightened pediatric peasantry.

His versatility as an investigator is illustrated by achievement in an ancient field of experimentation, the design of lures for fishes. The challenge came from the sophisticated salmon of the Margaree. There appeared on his desk beside the box of rickets slides another box containing a strange assortment of fur and feathers and, I am told, colorful items of enticement taken surreptitiously from Mrs. Park's hats. And again he reached eminence. There are various forms of fame. There is the Kober medal and in L. L. Bean's Catalogue there is a salmon fly listed as the Dr. Park.

After he had thoroughly demonstrated high effectiveness in research, opportunity to carry on was, in our best tradition, almost removed by the commitments which the headship of a clinical department imposes. Two years after his return from war service in France, as a pediatrician in the civilian division of the American Red Cross, he was given the Chair of Pediatrics at Yale and in 1927 he came back to Baltimore as Dr. Howland's successor following the lamentably early death of that beloved builder of a new era of pediatrics. The large loss of leisure for research was a severe deprivation. He did find time while in New Haven to carry out with Powers experiments which very beautifully illustrate the rickets curative effect of sunlight and the complete exchangeability of the environmental and the dietary factors. The conquest of rickets was now complete. But it was very untidy in that it came from recognition of only the initial factor of pathogenesis and left us with a fragmentary knowledge of the ensuing steps of perversion of the processes of bone growth. Dr. Park has been restive about this and has managed to contribute from time to time several important items of new information. Now that he has reached emeritus status and has whole days of leisure it is a joy to visit him in his laboratory and find him at work with the same zest and happiness as in his carefree early years.

We lament the loss to medical science which the limitation of Dr. Park's research imposed. But medical science is only a part of medicine, which is what we are trying to propel, and we find consolation in the contributions to the progress of medicine which Dr. Park has made over 27 years by his devotion to the various services which the word leadership implies. A host of younger men and women delight to acknowledge their debt to him for guidance and encouragement toward high objectives. This was provided, not by precept or advice, but by the best of all methods, informal companionship with an admired and beloved

chief. This he gave them with an unbelievable generosity even at the cost of his week-end leisure.

The Park family has always managed to live in a region of trees and birds. As a visitor to this home of limitless hospitality, I recall walks in the hills behind New Haven and in the woods at the end of The Valley in Baltimore, in the company of students, internes and young investigators. They learned a bit of ornithology by looking through Ned's binoculars, which they have perhaps forgotten, but what they saw through the prisms of his personality they did not forget. Doubtless they were astonished to find, behind a quiet demeanor, the gaiety of thought, sustained by whimsical fancy and a humorous use of allusion, which makes a letter from Ned a treasure which one tucks away for future chuckles. They found no trace of vanity. He permits his children to call him Punk and doesn't demur when they paint his Ford fire engine red. His humility regarding his own attainments is measured inversely by his always generous evaluation of the work of others, and it is perhaps relevant that the bird he most admires is the hawk. But beauty of personality is an ensemble effect and we must not desecrate it by further dissection. I have wished only to indicate the inevitable consequences of exposure of young susceptibles on those Sunday walks to the virus of aspiration, of which our friend is an innocent but a very notorious carrier. This was the Park model of the Groves of Academe. I am so convinced of the large gain which it has given to medicine that I have not grieved greatly over the dust which gathered on his microscope; there are so few Parks and Platos about.

While we have him teetering on Plato's pedestal, I will mention a quality of his thinking which I have always admired without limit. He has the rare gift of being able to dissociate, with remarkable clarity, idealism, which he serves, from ideology, which he abhors. This has given him firm position in asking for objective and temperate examination of deficits in the organization of medical care and for a cautious experimental approach to their removal. Being the least contentious of men, I am sure that he did not find this a congenial assignment. He met it with the same quiet, unconscious courage with which he used to contest his right of way against Baltimore traffic on a bicycle.

So, Ned, the Council, being unable to imagine how anyone could have served medicine along these several paths with a larger total effectiveness, has chosen you to receive the 1950 Kober medal. Along with it go the admiration and the affection of this group of your friends, the Association of American Physicians.

FIRST HARRIET LANE RESIDENT STAFF

1912-1913

Dr. Arthur L. Walters (Intern)

Dr. Eleanor B. Wolf (Stewart) (Intern)

Dr. William B. McClure (Intern)

Dr. Edwards A. Park (Director of Outpatient Service)

Dr. John Howland (Professor of Pediatrics)

Dr. Kenneth Blackfan (Resident)

COOPERATIVE RESEARCH EXPERIENCES WITH DR. PARK

E. V. McCollum
Baltimore, Md.

THE great good fortune of my having Dr. Edwards A. Park for a research co-worker came about in a way most unexpectedly. Our cooperative studies concerned the relation of rickets to diet. When I set up my rat colony in the newly founded School of Hygiene and Public Health at the Johns Hopkins University in 1917 I had no thought of undertaking any studies on the relation of diet to bone growth. Miss Nina Simmonds, Miss Helen T. Parsons, and I were occupied with further inquiries into the nature of the dietary deficiencies of certain natural foods and their milling products, and were especially concerned with inquiring into the defects of a diet which caused pellagra, since Dr. Joseph Goldberger had recently offered convincing evidence that pellagra was a deficiency disease.

During the decade which I spent at the Wisconsin Agricultural Experiment Station, Miss Marguerite Davis and I had demonstrated the existence of vitamin A, the first fat-soluble vitamin to be discovered. We had also made considerable progress in determining the relative merits, from the nutritive standpoint, of the naturally occurring mixture of proteins in certain seeds, the shortcomings of the inorganic nutrients in the seeds of plants, and had, in our study of the dietary deficiencies of polished rice, discovered that two classes of uncharacterized nutrients, one fat-soluble, the other water-soluble, were essential in addition to the basic constituents of the diet. We had demonstrated the superior nutritional value of the leaf as compared with the seed, and carried out the earliest studies which showed the nature of the supplementary dietary relationships among our natural and derived foodstuffs. There were many specific problems of this nature which, in my early years in Baltimore, we planned to study. These items are mentioned to make clear my own background of nutritional research.

One afternoon in the autumn of 1918 the late Dr. John Howland came into my office. He said he had just come from reading in the library and wanted to know whether I thought anyone had ever produced experimental rickets in animals. I expressed surprise that he should ask that question of me since he was a pediatrician and knew all that anyone knew of that disease, whereas I was a chemist and quite uninformed on the subject. I then said that Miss Simmonds and I had produced in young rats a condition which we thought might be rickets, and that we had such animals at the time. I invited him to accompany me to the rat colony, and there I asked Miss Simmonds to show the rats in question to him.

She chloroformed one of the rats and laid open the skin over the thorax, which revealed the "pigeon breast," Harrison's groove, and the calluses of healing fractures in the ribs, which

From the Johns Hopkins University.

form the "rachitic rosary." Dr. Howland exhibited great interest and said that the gross appearance of the thorax was quite like that seen in severe rickets in young children. "How did you produce this condition?" was his first question. To this I replied that I did not know what dietary factors were involved, and could only tell him the composition and sources of the ingredients of the diet. Then I expressed the belief that the problem was a soluble one, but that in order to discover the nature of the dietary defects which produce abnormalities in growing bones, as is the case in rickets, someone with expert knowledge of bone histology and bone pathology should examine and describe, histologically, the changes in bone structure produced by a wide variety of faulty diets which could be formulated in the light of experience and according to the biochemist's viewpoint. He at once said that he was willing to invest in the necessary histological work, and we tentatively agreed to undertake a cooperative project between the departments of pediatrics and biochemistry.

In the beginning Dr. Howland assigned Dr. Paul G. Shipley of his staff to supervise the cutting, staining, and description of bone sections, pending the return of Dr. Park, who was then in France in the Medical Corps of the Red Cross. Two technicians, Miss Madeline Spencer and Mr. James Joy, were housed in the Hunterian building and were given training by Dr. Shipley in the techniques to be employed. I set to work to lay out a comprehensive plan of feeding 30-day-old rats with a view of finding what in the diet is responsible for causing rachitic changes in their bones. We had just gotten well started in the study when Dr. Park returned in 1919. He and Dr. Shipley shared the task of describing bone sections and interpreting the pathological response of the anatomic elements to diets faulty in different ways.

Although rickets had been characterized as a definite disease by Glisson in 1660,[1] little was known about it until Pommer[2] in 1885 made extensive studies of the structure of rachitic bones. In 1890 Palm[3] reported the results of geographic investigations and pointed out the beneficial effects of sunlight in the treatment of rickets. Buchholz[4] in 1904 first called attention to the value of artificial light in the treatment of the diseases, but the value of his work was overlooked so that in 1919 the etiology of rickets was still a mystery. In 1919 Huldschinsky[5] reported on the curative action of the ultraviolet rays from a quartz-mercury vapor lamp, and the following year this was confirmed by Hess and Unger.[6] Schmorl[7] in 1909 had described in detail the manner in which calcium salts are deposited in bones in the healing of rickets.

At the time our cooperative studies were begun Dr. Park was thoroughly familiar with the clinical and experimental literature on rickets and related conditions. There were in progress independently in the department of pediatrics of the Johns Hopkins Hospital, studies on the etiology of rickets which were of great significance. Park and Howland kept puppies in confinement and observed whether such treatment would produce the lesions in the bones characteristic of rickets. Howland and Kramer,[8] about this time, began their studies of the phosphorus and calcium content of

the blood and plasma in normal and rachitic children.

Great impetus was given to the study of the etiology of rickets by the work of E. Mellanby,[9] who in 1918 published his earliest papers presenting evidence that rickets was caused by faulty diet and was specifically the result of deficiency of an "accessory factor" in nutrition. Mellanby first employed a diet of 175 c.c. of whole milk, with oatmeal and polished rice *ad lib.*, with 1 to 2 per cent NaCl, to produce rickets in puppies. Later he used a diet consisting of whole milk 175 c.c. with bread *ad lib.* Later still he employed a diet of skim milk, bread, yeast, orange juice, and NaCl. With these diets he induced bone abnormalities which he believed to be characteristic of rickets. As criteria he relied upon gross deformity, x-ray and microscopic evidences, and the calcium oxide content of the bones. He never described in detail the appearance of sections of the bones as revealed by the microscope. He was able to demonstrate clearly that certain fats, butter fat, and notably cod-liver oil, exerted a pronounced prophylactic value in preventing the bone lesions caused by his experimental diets. He established a standard diet which regularly produced rickets in puppies. Using this diet he tested many foods for their antirachitic value, or their ricketogenic effect. Lard, linseed, peanut, coconut, rapeseed, palm kernel, olive, and babassu oils were found to be ineffective, whereas cod-liver oil and butter fat exerted a decided action in safeguarding the bones against pathological changes. Addition of tricalcium phosphate did not afford any protection. Lean meat was found to exert some antirachitic action, but casein intensified the disorder. The higher the bread content in the diet the more severe was the rickets produced. He also tested cod-liver oil and butter fat which had been oxidized by passing heated air through the sample, a treatment which F. G. Hopkins had shown would destroy vitamin A. Cod-liver oil oxidized in this way was still effective in preventing rickets with Mellanby's diets.

The histological study of the bones of our experimental rats was based upon the characteristics of the bones in rickets as described by Schmorl: (a) calcification of the provisional zone of cartilage (intercellular substance) does not occur; (b) there is irregular invasion of the cartilage by blood vessels and connective tissue; (c) cartilage cells persist in the shaft below the normal epiphyseal line; (d) newly formed preosseus tissue remains uncalcified and is produced in abnormal amounts—the osteoid tissue; (e) there develops the rachitic metaphysis. Our criteria were limited essentially to the relationships of the different histological structures as they were modified by defects in the diet.

The experimental diets which we used were simple and complex combinations of natural foods. They were designed to permit varying the quality and quantity of the protein, the known vitamins, and the inorganic moiety. When we began to publish our results in 1921[10] we had completed studies of the effects of about 300 experimental diets on many hundreds of rats. The results indicated that, although the bones of young rats are highly responsive to dietary defects, the most significant factors for safeguarding normal bone growth were the ratio between the calcium and phosphorus in

the food, and the kind of fat supplied. Low calcium and high phosphorus, or low phosphorus and high calcium ratios were disturbing to bone growth, the former relationship causing rickets complicated by tetany. Feeding diets deficient or excessively rich in both these elements caused far less disturbances in bone histology than did unfavorable ratios. But with unfavorable ratios between calcium and phosphorus, rickets was not produced if the diet contained a small addition of cod-liver oil, or a large (20 per cent) addition of butter fat.

About the time we published our demonstration of these principles Sherman and Pappenheimer[11] described experiments in which they fed little rats a diet of white flour 95 per cent, calcium lactate 3 per cent, and NaCl 2 per cent, and observed that typical rachitic changes occurred in the bones. Rachitic changes, they found, could be prevented by reducing the calcium (lowering the calcium lactate), and adding potassium phosphate. This was a clear demonstration of the formation of rachitic lesions as the result of unfavorable ratio of Ca:P.

Dr. Benjamin Kramer made numerous determinations of calcium and phosphate in the bloods of our rats and showed that the blood phosphate was low in animals which showed rachitic lesions.

We oxidized both cod-liver oil and butter fat to destroy vitamin A and tested their effects in rickets-producing diets. We found that this treatment had little if any destructive action on the antirachitic factor, but these fats, after oxidation with a stream of hot air, were no longer effective in preventing or curing xerophthalmia, which is a specific lesion arising from vitamin A deficiency. It was from such evidence that we drew the conclusion that a second fat-soluble vitamin, an antirachitic substance, which we named vitamin D, existed. Both cod-liver oil and butter fat contain the antixerophthalmic vitamin in abundance, whereas cod-liver oil is very potent and butter fat but feebly potent in supplying the antirachitic factor.

We were able to demonstrate clearly that when little rats were restricted to one of our rickets-producing diets, and were exposed to summer sunshine in Baltimore for five hours daily, they were completely protected against rickets, whereas on the diet used they would in twenty-one days develop severe acute rickets when kept indoors. All observations on the effect of our experimental diets, when interpreted on the basis of thorough histological studies, were in accord with the extensive clinical studies which had been reported at that time which indicated that sunlight or artificial light containing ultraviolet rays would prevent or cure rickets in human subjects.

As has already been mentioned, Schmorl had in 1909 described in detail the histological pattern shown by the newly deposited calcium salts in bones during healing of rickets. We were able to produce, by the dietary defects mentioned, severe acute rickets in young rats in three weeks, and to observe the healing process histologically, under the guiding influence of the antirachitic substance, vitamin D. Hence we were able to develop a quantitative test for this vitamin based upon the extent of deposition of calcium salts in the line of provisional calcification in the long bones of little rats, rendered rachitic by feeding a

rickets-producing diet as part of a standard procedure.

Having devised the "line test" procedure for assaying food substances for vitamin D we were able to describe its distribution in nature. The basis of the Pharmacopoeial method for estimating vitamin D is the procedure which we described in 1922.

Cooperative investigations with Dr. Park afforded me the first opportunity to work with an expert in histology in the special field of bone pathology. By pooling our knowledge in the two segments of biological science which we represented we made discoveries which neither, working alone, could have accomplished.

Discussion with him of any aspect of our investigations never failed to stimulate constructive thought and open vistas which had not before been evident. I have never known a man with a more effective analytical mind in subjects relating to physiology and pathology.

But quite apart from the gain which I experienced in results of research, my association with Dr. Park was rewarding because it made me acquainted with a man unique in a number of respects. He narrowed his purposes to a degree which enabled him to point them directly at his mark, and saw relationships with unusual clarity. His intelligence was supplemented with insight such that I was frequently filled with admiration. One could invariably detect the seeds of judgment in his mind. He observed with unusual clarity objectivity and freedom from prejudice. No other man with whom I have come into contact has given me so satisfying a friendship as has he.

REFERENCES

1. Glisson, F., and associates: The Rickets, ed. 2, London, 1660.
2. Pommer, G.: Untersuchung Über Osteomalacie und Rachitis, etc., Leipzig, 1885.
3. Palm, T. A.: Practitioner 45: 270, 321, 1890.
4. Buchholz, E.: Verhandl. d. Gesellsch. f. Kinderheilk. 21: 216, 1904.
5. Huldschinsky, K.: Deutsch. med. Wchnschr. 45: 712, 1919.
6. Hess, A. F., and Unger, L. J.: Am. J. Dis. Child. 22: 186, 1921.
7. Schmorl, G.: Ergebnisse d. inn. med. u. Kinderh. 4: 403, 1909.
8. Howland, J., and Kramer, B.: Am. J. Dis. Child. 22: 105, 1921.
9. Mellanby, E.: Proceedings of Physiological Society, Jan. 26, 1918, J. Physiol. 52: xi, 1918.
10. McCollum, E. V., Simmonds, N., Parsons, H. T., Shipley, P. G., and Park, E. A.: J. Biol. Chem. 45: 333, 1921.
11. Sherman, H. C., and Pappenheimer, A. M.: Proc. Soc. Exper. Biol. & Med. 18: 193, 1920-1921.

EDWARDS A. PARK, YALE PROFESSOR 1921-1927

GROVER F. POWERS, M.D.
NEW HAVEN, CONN.

DR. PARK became the first chairman of the newly created full-time Department of Pediatrics in the Yale University School of Medicine on July 1, 1921. During the preceding academic year discussions took place relative to this development between Park and his colleague of Johns Hopkins days, Milton C. Winternitz, who had become Dean of the Yale school in 1920. On one of his conference visits to New Haven, Park was taken by the Dean to call on one of the strong supporters of the School, the Secretary of the University, Reverend Anson Phelps Stokes. Mr. Stokes is a tall, slender gentleman of courtly manners—most gracious and dignified. During the interview he thought it appropriate to examine the alumni file of E. A. Park, A.B. Yale 1900! Mr. Stokes rang for his secretary and was presently handed a folder in which he found—and read in an atmosphere of anticipation and slight strain—the following newspaper clipping dated August 25, 1905!

Dr. Park Completely Vindicated

The confession of Ralph Warner and John Kadra, two Massachusetts crooks, to the robbery of James J. Higginson's house in N. Y. on July 1 last, when $6,000 worth of jewels were stolen, has been joyfully received by Yale men in general, and by the class of 1900 in particular. It clears the name of Dr. Edwards A. Park, Yale 1900, the Higginson family tutor, who was arrested July 5 at Cristiansand, Norway, when he stepped off the boat with his mother and sister.

There were only three men of the 300 in Yale, 1900, who were more popular than Ned Park, according to the vote taken for the class book, and when he was arrested for the theft on a very slight clew his classmates raised a storm of protest. He was a society man, a member of the ivy committee, and chairman of the senior promenade committee, one of the greatest of Yale's social honors.

Such was the preinduction ceremony to a position on the faculty of the physician who was to be leader of pediatrics in the Yale Medical School for six years and for that period of time, Pediatrician-in-Chief to the New Haven Hospital!

In 1922, as a mark of special distinction, Park was appointed to one of the newly created Sterling professorships in company with Swan in Law, Cross in English, Seymour in History, and Warren in Geology. Park resigned his post at Yale in 1927 when he succeeded John Howland as head of the Department of Pediatrics in the Johns Hopkins University.

Dean Winternitz was deeply and effectively interested in Pediatrics and held that it should be one of the major disciplines of clinical medicine—not as was often the case at that time, a subsidiary division of Midwifery or of Internal Medicine. In the brilliant reorganization and rehabilitation of the Yale Medical School taking place in the early 1920's—new or reconstructed units of the physical plant, increased budgets, new faculty positions and appointments on full-time basis, major curricular changes—Winternitz was a dynamic and creative force and Park an eager and enthusiastic teammate.

In efforts and plans, the School had the enthusiastic and authoritative support of Yale's new President, James Rowland Angell; of the Treasurer, George P. Day; of the Comptroller, Thomas W. Farnam; of the physician member of the Yale Corporation, Dr. Fred T. Murphy; and of the Chairman of the Executive Committee of the New Haven Hospital, Isaac M. Ullman. Establishment of the new department was doubtless facilitated in many ways by the fact that Park was a forceful character in the Yale tradition and was recognized as such as an undergraduate.

Plans and funds were secured and allocated for a small full-time staff in pediatrics, for a modest new laboratory and office building, and for the conversion of a third-floor attic into a ward (III East) for general pediatric patients. In this ward were erected sixteen large glass cubicles; two ordinary rooms were assigned for care of premature infants; there was a milk preparation room and a small clinical laboratory for students. The second floor of the municipally owned "Isolation" building was used for the care of thirty-five children with infectious diseases.

Reflecting the emerging concept of the preventive and curative effect on rickets and infantile tetany of sunlight, there was built and attached to the general pediatric ward a large veranda which would accommodate the entire patient population even when each cubicle housed two patients!

On each pediatric floor and in the outpatient clinic there were installed mercury vapor quartz lamps; radiations from these lamps were under experimental study for possible preventive and curative effects in various diseases as well as in rickets and tetany.

With funds given by the General Education Board, an office and research laboratory building was erected on hospital property. The building was modest in its construction and simple in appointments but quite adequate in equipment and function; offices for the pediatric staff were located in one half of the first floor and laboratories for biological and chemical research occupied the entire ground floor. Contrary to the practice at Johns Hopkins at that time, technicians and assistants in research were available in both the biological and in the chemical laboratories.

In commenting on the temporary and makeshift physical facilities which were prepared for the new department, one may point out that activities are more important than buildings; modest as the plant was it provided the setting for the intellectual highlight of the Park regime at Yale, namely, the 12 o'clock daily ward conferences in which the entire staff and visitors participated. The group, varying in number up to twenty, was led by the tall, white-coated Professor who was accompanied by a retinue of colleagues of various ranks and physical dimensions!

To appreciate the drama of this noontime ceremony—a sort of "changing of the guard" affair—one must visualize the topography of the New Haven Hospital of those days. The Hospital occupies a large city block; *one* pediatric ward was on the third floor of a northeast building (and was served by stairway and by freight elevator); the *other* was on the second floor of a southwest building; the *offices* were on the first floor of the laboratory

building situated midway, approximately, between the two wards. The "Pediat Parade" started in Dr. Park's office, proceeded down a long central corridor and up two flights of stairs; or in the other direction—not quite so far but across an open court, often in rain or snow—and up one flight! Some "rounds" went in both directions on the same day! They usually lasted until 1:30; Frank Babbott often treated staff hypoglycemia with dried raisins or chocolate bars! The intellectual repast was always rewarding especially when buttered with pertinent Park stories—rarely previously told or repeated (except on request). Every patient on the service was sooner or later submitted to meticulous and often repeated examinations and discussions. Dr. Park, hands above his head clasping the curtain rod, ever resourceful and erudite, led the debates; everyone was stimulated to present his findings, his ideas, his point of view. The discussions, please note, embraced medical and social care as well as diagnosis and scientific data available and called for as a result of the deliberations. One of the interns of those days, Professor Daniel C. Darrow, has written:

> To an intern, Park presented the picture of the scholar rather than the practitioner as a professor of pediatrics. He always wanted to know first what other students of disease had written on the subjects suggested by a patient. Second, he wanted to know how observation of the patient could advance the knowledge of disease. I felt that the minute observations were often futile and of necessity inadequate to acquire the necessary facts. However, nothing could be better in revealing inadequacies of our knowledge to students and house staff. The observations were within the grasp of the students and the difficulties of gathering information so apparent that the curious were driven to other means of study. I believe we all got the feeling that each patient presented an opportunity to learn from the literature and, if we were smart enough, from planned observations of the patients or in laboratory experiments.

Dr. Park once told the author early in their New Haven careers that the Yale service was too small to be as valuable as are larger services in evaluating therapy but served well as a basis for developing ideas on disease and child care. Subsequent developments at Yale seem to have shown that the principal handicap of a small service is simply that it cannot provide adequate facilities for a *large* staff and a *large* student body and for those who require bigness for their contentment. The highlight of Dr. Park's service to pediatrics while at Yale lay in the fine quality not only of the scientific study of disease but in the emphasis on the broad implications, social relationships, and public health correlations of child care. And these "ward rounds" constituted the forum in which ideas were brought forward and concepts and principles crystallized; this, in the writer's opinion, is graduate pediatric education in its most effective and significant form!

Dr. Park and his staff at his urging presented their data and their ideas at many meetings of scientific and nursing and public health assemblies. The author recalls several all-pediatric, all-Yale programs. Park often forgot black shoes or bow tie for formal dress but never the ideas he wished to set forth! Park believed in the importance of travel and stimulating contacts; he visited other clinics and scientific institutes frequently and was usually accompanied by one or more of his staff colleagues. Early in his Yale professorial career (spring of 1923) seeking

new ideas he obtained leave of absence in order to visit European clinics. On this trip he also served as official Yale delegate to the Pasteur Memorial Celebrations at the Universities of Paris and Strasbourg. He returned with many unique and valuable suggestions regarding diagnosis and therapy.

Finkelstein was clearly the professor whose teachings especially fired Park's imagination. Finkelstein's large volume on the nutritional disturbances of children was the text for many informal Yale staff seminars on infant nutrition; likewise, Claude Kerr's splendid treatise on fevers furnished stimuli for fascinating discussions on infectious diseases. Sheets of ruled paper, three to four feet in length, were purchased, and on these columnar recordings were made in minute detail of the clinical phenomena observed in patients with various diseases—a sheet or more per disease. In addition, there were long, detailed descriptions of patients and analyses of case histories of special interest as well as staff conferences at which these were reviewed. Bedside charts were designed for the meticulous recording of relevant data for each patient, including measurements and graphic representation, often in color, of the composition of milk mixtures and other foods. All data were expressed in metric nomenclature from the outset—not a common practice at the time. With infinite patience efforts were made to correlate these detailed data with signs, symptoms, and natural history of disease; clinical studies resulted from these observations and correlations. How nearly impossible this type of clinical study and interpretation would be today when therapy, often blind, antedates careful diagnosis, and the natural history of disease is thereby frequently not observed!

The outpatient service was Park's area of special clinical interest during his first tenure on the Johns Hopkins faculty and as director of the dispensary established at LeHavre (1917-1919) by the American Red Cross during World War I. He had definite ideas concerning the high service and educational values of outpatient work; these were revolutionary and required administrative implementation which was not forthcoming at the Harriet Lane Home. In New Haven, however, he could give imagination and administrative skill free rein with full support from Dean Winternitz.

Under the Park regime, the outpatient clinic was to be active all day; sick and general patients were cared for in the mornings; special clinics for patients with syphilis, heart disease, allergy, and tuberculosis were in session in the afternoons as were well-baby conferences. In France, Dr. Park had established a dispensary program in which children were seen and cared for on an appointment schedule so that parents were handled with respect and consideration for their other responsibilities, their children given careful, unhurried examination and well-considered treatment, and the maximum educational values of the work made available to the attending physicians, nurses, and social workers. This system was established in New Haven as one of Park's first administrative acts. The attendant problems to be solved were difficult since the dispensary building was across the street from the hospital and administrative and professional integration was lacking as was subsidiary personnel. Neither the all-day outpatient

FIRST FULL-TIME YALE STAFF IN PEDIATRICS

Seated, from left to right: (1) Ruth A. Guy (Mrs. Francis R. Dieuaide), instructor whose principal area of interest at the time was allergy; subsequently in charge of pediatrics in the Peking Union Medical College.

(2) Ethel C. Dunham, instructor who was chief of pediatric dispensary and carried on studies in tuberculosis; subsequently consultant to U. S. Children's Bureau and authority on premature infants and their care.

(3) Grover F. Powers, assistant professor and Park's successor at Yale.

(4) Edwards A. Park, Professor and Chairman of Department.

(5) Alfred T. Shohl, Associate Professor and Clinical Chemist; subsequently associated with medical schools of Western Reserve and Harvard. (Deceased.)

(6) Martha M. Eliot, instructor and first resident; subsequently director of rickets prevention project and now Chief of U. S. Children's Bureau.

(7) Marian C. Putnam, intern; subsequently child psychiatrist at Yale and now director of the James Jackson Putnam Children's Center for emotionally disturbed children.

Standing: (1) Ernest Caulfield, intern; subsequently pediatrician-in-chief, Hartford Hospital; outstanding authority on the history of Pediatrics.

(2) John C. S. Battley, assistant; subsequently associated with Henry Ford Hospital and now in private practice.

(3) Frank L. Babbott, Jr., assistant; subsequently President, Long Island Medical College.

(4) Joseph Weiner, intern; now in private practice.

session nor the allocation of special periods to sick and to general patients on the one hand and to those with previously diagnosed chronic or subacute diseases on the other, nor the examination of all patients at an appointed day and hour were procedures currently practiced in institutions of that day. The setup was somewhat of an innovation.

The pediatric dispensary at Yale as at Johns Hopkins was directed by a full-time senior physician as chief-of-clinic with assistance from voluntary workers and from members of the house staff. The importance of nursing education and supervision, medical social service and visiting nurse cooperation were always stressed by Park; he was an enthusiastic supporter of Deans Goodrich and Taylor in the establishment of the Yale School of Nursing.

The emphasis in undergraduate teaching in clinical medicine at Yale was placed on the clerkship—in pediatrics as in the other major disciplines—and on small, informal, intimate bedside conferences with an instructor. The pediatric clerkships were not elective and they occupied in the aggregate about one-half of the time allocated to internal medicine or to surgery. An innovation at the time was the assignment of third-year students to bed patients in the hospital and fourth-year students to ambulatory patients in the dispensary—a reversal of the usual order. In pediatrics there were daily informal bedside teaching "rounds" for students conducted by the senior staff members and a weekly clinical lecture given from time to time by various teachers. The voluntary members of the staff assumed major responsibility for teaching of fourth-year students on hospital rounds. There were several elective courses offered and well attended on growth and development, infant nutrition, bedside procedures, chemical techniques, and child welfare. Attendance at the special outpatient clinics was elective. All students before graduation were required to present and have accepted a thesis on a subject of their choice and developed under faculty supervision. Pediatrics had its share of students preparing their theses under departmental guidance; several of these were later published in scientific journals.

The pattern of clinical teaching in all major departments of the Yale school was fundamentally the same and Park shared responsibility with the Dean and other colleagues in developing the program just outlined. The program was very different from and more to his liking than the one to which he was accustomed in pediatrics at Johns Hopkins.

The Department of Pediatrics at Yale under Park was research oriented in that there was a pervading questing spirit at all times and in all areas. The emphasis was on intellectual curiosity more than on oral or written reporting of accomplishments although these were never neglected. The written evidence as revealed in the bibliography covering the six "Park Years" is of pathological studies of experimental and human rickets, chemical studies of electrolyte disturbances of rickets and other diseases, clinical studies, and projects relevant to the social and public health aspects of pediatrics.

Park had worked with several colleagues in Baltimore in various departments and on almost all aspects of ex-

perimental and clinical rickets and on scurvy; his special interest at Yale was on the effects of radiant energy, cod-liver oil, and bile on the disease in infants and experimental animals. At Yale, Park was midway in the path which led to his present high eminence as a foremost authority on bone pathology. The radiations of the mercury vapor quartz lamp and the effect of various filters in respect to these radiations were investigated.

The major studies in electrolyte metabolism dealt with hydrogen ion concentration of gastric and intestinal secretions in various clinical conditions and electrolyte disturbances in infantile and experimental rickets and tetany. Here was laid the groundwork for a future publication by Alfred T. Shohl of an excellent monograph on mineral metabolism.

The clinical studies were concerned principally with the efficacy of radiant energy in the therapy of various diseases, infant feeding, caloric analyses of constituents of milk mixtures, value of transfusions of blood in treatment of patients with diarrhea and other diseases, therapy of diarrhea, use of laryngeal suction in diphtheria, demonstration of calcification in tuberculous cervical and abdominal lymph glands by roentgenograms.

In the domain of social and preventive medicine, attention has already been directed to the establishment at Yale of the appointment system in the operation of a humanitarian and educationally effective outpatient service. A second outstanding contribution in this public health area was a three-year project undertaken in cooperation with the New Haven Health Department and the Visiting Nurse Association and with the support and sponsorship of the Children's Bureau of the United States Department of Labor, Grace Abbott, Chief. The purpose of this joint enterprise was to demonstrate whether or not as a practical public health measure infantile rickets was an eradicable disease. A district in New Haven largely populated by persons belonging to the highly vulnerable Negro race was selected in the summer of 1923 as the study area. All newborn infants were registered in a special local clinic and given medical and nursing examination and supervision. Monthly physical examinations were made of these babies and also roentgenographic studies. The chief antirachitics advised were cod-liver oil and sun baths; infants in other New Haven districts served as controls. The roentgenograms were reviewed along with clinical findings by Dr. Park and the Rickets Study staff twice a week.

This Study established the fact—one now so simple and clear—that infantile rickets is a completely preventable and curable disease in the population of a country! Demonstration of this fact was of tremendous importance in preventive pediatrics and practical public health especially at a time, quite different from the present, when rickets with its many disastrous effects on child health was rampant in babies living in Northern latitudes! Forthwith, the universal use of cod-liver oil in the feeding of infants and exposure to sunlight were emphasized in the widely disseminated Children's Bureau booklet, *Infant Care;* the ensuing beneficial results to child health are of incalculable magnitude. Of course, in a short time many other forms of antirachitic therapy were available and were prescribed.

Concerning Park himself, this Study is particularly revealing for it shows the man who was apparently interested principally in the minute details about rickets was the one who planned the practical extension of the new knowledge so that rickets was abolished.

Dr. Park was always able to attract competent men and women to his staff whether in medicine itself or in its ancillary fields; he was a vigorous proponent of the role of women in medicine and his first resident was Dr. Martha Eliot. During his six-year tenure at Yale some thirty to forty physicians were associated full time in one capacity or another with his department; most of them have achieved positions of leadership in some aspect of the broad domain of child health.

Park insisted on giving his staff members a high degree of personal responsibility in the various professional situations in which they became involved in line of duty. For the writer, the burden was too great at times to be borne with equanimity; he recalls an amusing experience illustrating this Park characteristic—and also stubbornness in both parties in equal degree! Near midnight once upon a time, Dr. Park was called by telephone in order that there might be an urgent consultation. After prolonged ringing, there was no answer and in time a colleague was dispatched by car to deliver the message in person to the reluctant consultant. On arrival the telephone was still buzzing vigorously, receiver detached, and a much irritated Professor was found trying industriously to muffle the instrument with blankets and by closed doors so that the household might resume their slumbers! It should be added that Dr. Park was in the throes of a prolonged literary and scientific composition when this episode took place!

During his early years at Yale, Park lived near Lake Whitney about four miles from the Hospital. Later he lived in Glebe House, Brooksvale in Cheshire; the house was beautifully situated on a trout stream and was thirteen miles from the New Haven Green. Transportation for the Professor was usually by bicycle, the rider often clad in a yellow oil skin suit; nevertheless, he seldom arrived at his office later than 8 or 8:30 A.M. Evening medical or faculty meetings meant midnight rides not infrequently in rain or snow—but one heard only, characteristically, of the beautiful nights when moon or stars shown brightly and clearly!

The Park lunch was usually a sandwich eaten in company with colleagues; there were many never-to-be forgotten cracker barrel discussions of chess or poetry, polities or history, medicine or trout fishing! (The salmon seems, to the writer, to be a later object of piscatorial interest to the Professor.)

Professional visitors were frequent and numerous and always recipients of gracious Park hospitality, informal and natural. One dignified British guest, following the custom of his country, placed his shoes outside his bedroom door expecting them to be shined! They were—by the Professor himself! However, the visitor did not appear for breakfast at the appointed time; inquiry revealed that he had but one shoe although two had been returned after the professorial shine! Search at long last disclosed the missing mate in the clothes hamper where it had been hidden by a mischievous Park youngster!

Sunday afternoons were given over to picnics at the Park home or to hikes in the nearby countryside—everyone invited, informality and good-fellowship the order of the day. In those days Park was tremendously interested in football and autumn week ends were festive occasions at Glebe House with guests from far and near—old classmates and professional colleagues! The first order of business at Monday cracker barrel discussions was a post-mortem examination and argument over the Yale performance in the Bowl on the preceding Saturday—and there were many Park suggestions which the coaches would have found of great strategic and tactical value!

Of these inspiring years, the writer and many others treasure most happy and grateful memories!

CHILDHOOD DAYS

MARION EDWARDS PARK
PLYMOUTH, MASS.

MY BROTHER Ned was born and brought up in upstate New York, in Gloversville, then a village, high above the Mohawk Valley and on the southern foothills of the Adirondacks. His father, William Edwards Park, had gone there as the Congregational minister two years before and was to stay on in the church twenty-five years more. The village was young; it had sprung up in the sixties when the Union Army needed heavy gloves and the near-by North Woods offered a handy supply of deerskins. Naturally that source soon failed, and in our childhood hides were being imported from the West and from South America and the local glovemaking was already concentrated in small factories.

Ned's father, who was an ardent amateur historian and was accused by his congregation of never preaching a sermon without mentioning Alexander, Caesar, or Napoleon, was deeply interested in his new neighborhood. With the Mohawk Valley only ten miles away brimming with the Five Nations, the Jesuit missionaries, and the Revolutionary War, Gloversville had on one side Johnstown, a very early settlement where Sir William Johnson, one of the great men of the Colony, had lived and reigned, and on the other Kingsborough, settled early by a minister and his flock who had migrated en masse from Connecticut.

He was almost equally interested in the near-by hunting and fishing. He often spent his vacation at the then completely wild West Canada Lake and we occasionally followed him as far into the woods as my mother thought a civilized family could go. Ned in his turn as a very small boy began to fish in the trout brooks which were within walking distance (and put the mileage high!). We children had to write Sunday letters to our grandfather and the recipient reported that for years Ned's were identical with a conscientious change of numeral: "Dear Grandpa, I went yesterday and caught five. Your aff. grandson, Ned." In the long winters the coasting on the steep hills was superb but the heavy snowfalls often interfered with skating. Toboggans and snowshoes were at hand but skis had not yet crossed the Atlantic.

The parsonage was a commonplace comfortable house on Main Street; we maintained a handsome but stupid setter, a succession of cats (one named Maltie Blaine and Logan Protection High Tariff, which hints at our political affiliations) and an occasional rabbit or canary. The families in the church were largely descendants of the Connecticut migrants with a few expert English and German glove finishers added. Parents and children had pleasant friends. There were few excitements and no spectacular crises of pleasure or pain. Our simple environment could have been matched, I am sure, all over the eastern states. It was a good beginning.

Ned's parents, however, had had a different though perhaps an equally typical kind of American childhood and we had a taste of that too. They were both children of professors at the Theological Seminary in Andover. Ned's Park grandfather, the son of a Brown University professor, was president of the Seminary and, I gather from his friends and foes alike, a kind of Congregational pope wherever the conservative faithful were gathered. He lived to be over ninety, an acute, powerful, and witty old gentleman as we knew him. He had married a great-granddaughter of Jonathan Edwards, brought up with her ten brothers and sisters in the Catskill Mountains where her father had a large tannery and her mother acted as nurse and doctor for the little community of Colonel Edwards' workmen, even venturing, we were told, to cut off a man's leg in some emergency. My picture of our grandmother's childhood was plenty of wolves and bears and no school but I probably have remembered what I wanted to. Ned's mother was also an Edwards but somewhat to her relief, I think, of a different family. "No fun naming him," his father is reported to have said when Ned was born. It had been the correct thing apparently for a minister to marry into his own profession and on both sides the lines went back through New England ministers. There were variations as well as sameness, however, and Ned's mother had retired in disgust from a brief excursion into family genealogy when she ran on a forefather who was fined a shilling for stealing a canoe. Between the Clergy and the Criminal, there were, of course, others —farmers, lawyers, teachers, and colonial officials—but, so far as I know, no doctors show up. However, one of Ned's early inquiries, "If a man had 'ralgia and leprosy and the disease the man had who tried to get the bed away from Jesus, would he die?" seems to indicate that he was turning early from theology to medicine.

His Edwards grandfather died when his mother was small and we knew him only through her lively memories. A country boy from a Connecticut valley farm, he grew up with delightful tastes—out-of-doors, travel, wide nonprofessional reading, especially English poetry and Shakespeare. He taught his children to wander in the lovely country around Andover; he took them to Europe for a long year and himself got as far afield as Egypt and Palestine; he named his son George Herbert and took his little daughter to Rydal Mount to see Wordsworth. His way of reading aloud the poetry he loved to his children Ned's mother followed and we accordingly in our generation listened—liking the sound when the sense was beyond us—especially to the poets of the Romantic Period, to the Faerie Queene, to all the shorter Milton poems, with a dash into Paradise Lost. And I feel sure that it was his grandfather's love for the cadences of the English Bible which we heard when our mother read it. He taught her, too, the value of learning poetry by heart, a poem a Sunday, with a family recital Sunday evening.

Ned's mother herself was a delightful person to live with—intelligent, superhumanly wise with people, affectionate, and amusing. She was devoted to Ned, and to her casually kept

notebook I owe the recording of his remarks. She spoke and read French like English for she had been three years at school in Geneva. In a day of nonathletic females, she had done "high walking" everywhere in Switzerland, including the three-day "Tour de Mont Blanc" and, what seems even more remarkable, she had walked the twenty-three sea-level miles from Andover to Boston. After her father died, her mother, a pupil of Mary Lyon, started a school for girls in her big Andover house. Our aunt and eventually our mother taught in it. Grandfather Park and his confreres in the Seminary lectured on the Bible and Shakespeare and what-have-you, and Grandmother Edwards, though inexperienced and completely unworldly, managed to build up so good and so successful a school that starting from scratch she could educate her children and lay by enough to help her grandchildren with their education.

We ourselves were in Andover a good deal, at one or the other of the two near-by houses on the elm-bordered street. Indeed, when Ned did not especially like the Edwards breakfast, he would beat it to the Park breakfast table. The children we played with were as clever as they come; Boston and the North Shore were not too far away and the swing between winter and summer stirred us up at both ends.

The so-called main business of children going to school was confined, of course, to Gloversville, though home training through the family practices of reading aloud and of good talk was never stopped. At first our mother taught us, but soon we trudged up the hill across the street to the public school where we progressed duly from one dull room to another with only a few rays of light. Ned went to a boarding school in the Berkshires for one year when his mother was anxious about his adolescent moods, and he had a final year at Phillips Academy before he entered Yale along with two of his early fishing cronies. Both school and college were chosen, I think, because his father had traveled that road, and I suspect neither one contributed much to the seriousness and absorption in his work which came later. His mother who thought she had seen those qualities clearly in the small boy was disappointed. He graduated from Yale in 1900, and after a year of tutoring in Michigan, he suddenly, to us, decided to enter the P. & S. where we saw he caught fire. The family watched, at first in surprise, but with complete approval.

I doubt neither the poetry nor the truth of Milton's "The childhood shows the man, As morning shows the day," but I find it difficult and even dangerous to apply it to my brother. The only scholars in Ned's background, I think, were theologians and their working ways I am entirely unfamiliar with. I can guess, however, that the minds of experts are built similarly. They must have the power of absorption; part of their equipment is the magically quick recognition of what is important and this carries with it as a corollary the ability to ignore everything else in the field of study and also in human relations which takes precious time. The only family hand-me-down about Jonathan Edwards is that he did not know his own children on the street, and the only theological expert I ever knew —Grandfather Park—was wholly ar-

bitrary in his absorption in his work and in his complete disregard of everything he chose to think unimportant. Scholar and child dismiss outside areas abruptly. Ned once said to his mother, "I have been thinking about what I should do after I die. I don't want to go to Hell and I am not interested in Heaven." Meticulous honesty and persistence the scholar must of course have, and my guess is that if his subject is not completely abstract, but touches the field of human life, or if he must communicate with men and women, if for instance he is a teacher, he must add the power of quick and clear understanding of other minds. And unless he is superhuman, he needs the stimulus of discovery.

I do not know whether anything I have said reproduces for later friends of Ned anything of the small boy. He himself could do his portrait better. Once when in the pride of greater age I reproved him for saying he remembered something that happened before he was born, adding with finality, "I know two years more of things than you do," he replied, "I was in Heaven then and God could tell me more than you could find out here." Unfortunately for me, this has always been so.

THE CHIEF

ROBERT COLLIS
DUBLIN, IRELAND

ONE day in the early fall of 1927 when the clear American air seemed the essence of life itself, I stepped into the gloomy hall of the Johns Hopkins Hospital, and enquired from a formidable lady receptionist who sat under a still more formidable white marble statue of Christ where I would find Professor Park. I was directed to the Harriet Lane Home and proceeded down a number of corridors, through glass swing doors, and turning right found myself in an outer office in which sat a young lady with dazzling eyes. She rose at once and received me with such charm that the nervousness which had steadily increased for the last five minutes left me. Miss Richards, for it was no other, passed me on through an inner door into a second room where a tall rugged man dressed in a very long white coat was standing talking to another person dressed similarly. The tall man held out a great hand and took mine with much friendliness: I looked at a bronzed face and into two of the kindest and most comprehending eyes I had ever seen, and realized with sudden prevision that I was in the presence of a nobleman of his country, a man of Lincoln-like greatness who wore no mask and whose only protection from the world was a shield of absolute honesty through which the darts of malice could hardly pierce. So immediate and vivid was the impression of the scene upon my mind that now after twenty-five years I can see it clearly, even to the very photographs upon the walls of his study. Perhaps it was partly because I had come from such a different world. Some two years before, Still had made me his last resident before he retired from the Hospital for Sick Children, Great Ormond St. Here I had looked after the beds of the three senior physicians: Still, himself, Robert Hutchison, and Hugh Thursfield. They belonged to the previous age of great clinical observers and teachers and to the world of London specialists. Still always wore impeccable hard white shirts and collars, and a professional suit with a short black coat, and Robert Hutchison a gray frock coat which was decorated at every round by a carnation presented with due ceremony by a child in the ward.

Both had started as poor boys, one Cornish, one Scottish, and had fought their way into the very heart of the English professional hierarchy, assuming in so doing the veneer of English milords while hiding behind their elaborate masks two very different personages. Only once in all the time I had known Still had I caught him off his guard. I had called him to a case of primary peritonitis in the late evening when the formidable sister of his ward was off duty, and then had myself been called away on another errand after his arrival. On coming back into the ward I found him sitting playing with a couple of children who had awakened. He looked someway pathetically lonely as he sat there and I

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wondered why he had no children of his own. He did not move but beckoned me to his side. That evening he stayed at the hospital for a long time and talked to me of his cases, his worries about them, and his book which he was then writing. Next day his impenetrable mask was up again.

These great English physicians had been the pioneers of clinical pediatrics but they were almost unaware of the scientific approach of such great centers of thought as the Hopkins. They belonged to a system whereby no physician's opinion was ever directly questioned by another, each being a god in his own right.

Here then for the first time I met a new kind of teacher, one who found it possible to be himself quite simply.

I presented myself and asked how I should get started.

"I've only just got here myself" he said, "and I guess it will take a little time for us all to find our feet."

He enquired if I was fixed up for living quarters in the university dormitory, showing a consideration for his juniors with which I was quite unfamiliar.

Then having introduced me to the other person he had been talking to as one of his associate professors, he suggested to him that he might like to show me round. When the latter accepted the suggestion readily and took me and himself off on an extensive tour of the Clinic it seemed to me that Park showed a sign of relief.

We soon met Emmett Holt, the other associate professor, and the son of the famous old Holt, Still's counterpart in America, and then a string of others: a man with a wide smile and very intelligent eyes who seemed balanced and at peace with himself like Park, Rustin McIntosh; a restless Swede of the curious name of Dr. Count Bengt Hamilton who made me feel uneasy; Hugh Josephs, a research worker of fame; an alarming little man with an unpronounceable Hungarian name, and a lot of residents, among the latter being a shy lady doctor with a diffident smile, Helen Taussig.

Gradually we all found our places with Park's guidance. Everybody had to have his own research problem and at the same time carry out a certain amount of clinical duty either in the wards or in the outpatient department, and all meeting each day for grand rounds at twelve o'clock when a case or a group of cases would be discussed in detail.

It was no easy job to weld such diverse material, and one so bristling with individuality, into a team but Park managed it in an extraordinarily short time using methods unknown either to European Herr Professors or Harley Street specialists. He brought us out to his house along with some of the secretaries, technicians, and others, where we met each other informally and where we rapidly began to appreciate each other through a growing loyalty to him. He called us all by our Christian names and seemed to expect us to do the same to him. Someway the newcomers like myself felt that that was not quite the thing. Instinctively we felt we wanted to build him up, even if he did not seem to care; perhaps for our own sakes as much as his. But we could not call him "Dr. Park," less still "Professor." It just did not sound right even on Bengt Hamilton's lips. In the end I called him "Chief" and "The Chief" he became to us all from then on. Though

in our hearts we thought of him as Ned even in those early days.

Gradually these meetings at his house became a regular feature of our lives and we would meet at "La Paix," a simple wooden house on the Towson side of Baltimore, which itself was in the large grounds of a big house with grass lawns and a pond. We would foregather there on Sunday and then go for a long march into the country on foot or on horse, cook our lunch, and return to "La Paix" late in the evening to cook scrambled eggs for ourselves in the Park's kitchen. Mrs. Park had a very difficult time as The Chief often forgot to tell her how many were coming, though as a rule Miss Richards would get a note to her beforehand by way of his pockets without him ever being aware of this clandestine correspondence. Soon Mrs. Park also became part of our lives as did their children, Sally, Rollo, and David. They called their father Punk and their mother Moo and she became Moo to us, and has remained Moo for a quarter of a century, so that on meeting the Professor of Pathology at Bristol, or Sir James Spence in Newcastle, I will enquire, "How is Moo? Have you heard from her lately?" The children, of course, added greatly to the pleasure of those days. They were high spirited and gay. I taught Rollo to ride well and there was the occasion when one of Sally's lady teachers—she had a disturbing habit of bringing them along on picnics—was charged from behind by a bull calf when bending down to pick up a baseball. And the occasion when they painted their father's old Model T Ford bright red and we drove frantically through Baltimore, blowing the horn so that the police on point duty waved us through thinking we were a car belonging to the fire service, and then shook their fists with amused Irish grins when they discovered their mistake too late.

In the evenings we threw away the last remnants of our masks and each did what in his heart he had longed to do but had never dared before. McIntosh played for us divinely on the piano while we sat in the mottled light of a log fire—I can still hear the notes of Schumann's carnival as I write, which he would play from beginning to end without music almost in the dark. I would read them the Irish poetry I loved best. Park who had a passion for the battles of the American Civil War would read of Gettysburg: Picket's Charge, Longstreet's indecision, Mead's unexpected victory, so that when we visited the battlefield we met Little Round Top and Big Round Top as old friends. For hours we would suddenly talk shop, discussing scientific problems, or remain silent, each at peace.

Meanwhile work proceeded apace in the department. We arrived punctually at 9 A.M. and worked morning and afternoon, Saturdays included. The latter I found very difficult to get used to, having always since I was weaned kept Saturday afternoon sacred to recreation. However, so keen was our competition to make the department a success that whenever I took a Saturday afternoon off I felt guilty. This spirit in his department was entirely created by Park himself. One day he came into the rather crowded, dull, outpatient clinic where I was working. "Bob," he said, "there is a promenade concert at 4:30 P.M. If you go off now you could hear it; I'll finish your clinic for you here." I knew he

wanted to go himself quite as much as I did. I looked at him. I felt for a moment I should refuse but then realized that it was my duty to obey and try to understand. All I could do was to try and find some unpleasant job that needed doing in the department or at the Park's home and do it later without telling anybody so as to get even with myself.

Personally I found the American methods and the Johns Hopkins' somewhat superscientific approach a little difficult to assimilate quickly after Still who had jumped on his assistants if they hurt a child by one unnecessary prick. It was not till later that I realized how much I had learned in mental honesty by the naked scientific method of approach there. One thing I could never get used to, however, was ruthless animal experimentation. Once when Rivers was taking me round the Rockefeller Institute in New York he said, "Let me show you our wonderful animal house." There I saw row after row of creatures crouching behind wire netting, the horror of terror in their eyes, while cold scientists watched their reactions. "Marvelous, isn't it?" he said as we came out. "Yes," I said, "but I'm not too sure—the end doesn't justify the means you know, and though animals themselves may not know compassion, we do. Don't ask me why. But we do." And then little thinking that I should see my words come true, I said, "If we're not careful we'll be calling some group of people 'inferior animals' and putting them in cages and doing experiments on them!" That was before *Mein Kampf* was heard of. I told this story to Park. He smiled. "Yes," he said, "you upset little Kajdi terribly the other day when you said that taking blood out of a live rabbit's heart wasn't fair on the rabbit. He said the English were lunatics with their sentimental laws protecting animals." Park seemed to understand what I thought and what Kajdi felt at the same time.

For the last four months at the Hopkins during my second year I stayed entirely with the Parks. These were some of the happiest months of my life. Once a week I organized a paper chase on horseback before breakfast when we would gallop through the American woods in the cold fresh morning air as the sun was rising like a red ball through the early mists. I would return to La Paix, full of energy and vigor, breakfast, and then drive the Chief in his old barouche to the Hospital. On these occasions he often talked to me about the problems of his department, or his thoughts upon life, religion, and politics.

Some people said that Park's only real weakness was a failure to dispose of failures in his department, that he helped his good assistants to get better jobs elsewhere and was always left with the second rate. It is a matter of opinion whether the highly successful department which turns out a steady stream of high-class published work under a Herr Professor of fierce discipline and unapproachable grandeur is ideal. We all know such departments and the published work is often not all that important either. Or whether Park's method activated by a surpassing humility and humanity which means the carrying along by the strong of some of the weaker brethren so that the idea of service shall not be forgotten, does not in the end lead to finer results. Park was himself a scientist and believed in

his soul in a dedication to the pursuit of knowledge as the highest ideal. He would have loved to bury himself in his laboratory and work long hours into the night enthralled by the pursuit of an idea toward its source. Hence the position of Chef de Clinique irked him a good deal, and sometimes he would say to me with extraordinary humility that he wondered if he was really the best man for the job.

Once he said he felt he should take the summer off and read a European textbook on Pediatrics right through to fill in the missing chinks in his knowledge. It surprised me to know that he had chinks and more that he should tell me so. I could not possibly have imagined anybody in London, save perhaps Still, daring to criticize himself to that extent, and even the latter would never have spoken of it to a junior. Now having reached the same age as Park was then, I realize how profoundly important such an exercise is for all of us, and have in fact myself just completed a similar discipline.

Park was a person about the farthest removed from politics that it is possible to imagine, yet his comments on the politics of the time were worthy of respect. He regarded Mr. Coolidge's lack of pronouncement as not necessarily a sign of hidden wisdom and he did not in any way regard Hoover as related to God. Hence though of fundamental New England stock and in no great sympathy with the romantic and gallant gentlemen of the South he was inclined to think that the Democrats might have some of the answers. He regarded the increasing vulgarity of moneyed power unrestrained by responsibility with foreboding. It is as dangerous to call a man "liberal" in Washington today as it is to call him "middle-class" in Moscow, so all labels are best omitted when describing Park's attitude to affairs and to fall back upon a very old and now not often used term, and say that he seemed motivated by righteousness, if the word can be removed from its usual religious association. Park was not religious in the ordinary sense. Protestant preachers mouthing their texts from ancient Jewish scriptures, which if analyzed were often completely meaningless out of their context, had sickened him in his youth, and the Holy Sisters in a Roman Catholic hospital, in which he had worked for a time, with their beads, their colored images, and their prayers to the saints had not attracted him to Catholicism either. He believed in truth and I have no doubt he will find its meaning in the end.

I learned more from my association with him than from any other teacher I have ever known, and I am forever grateful for his great generosity to me.

On my last day he drove me to the station. I said good-bye with such pain in my heart as I have seldom known, and seeing him tall and solitary amidst the crowd of ordinary people I realized that I had parted, from what my old mother would have called, *a very great gentleman.*

BIBLIOGRAPHY OF DR. EDWARDS A. PARK

1. An Experimental Study of the Resistance to Compression of the Arterial Wall. Janeway, T. C., and Park, E. A., Arch. Int. Med. **6**: 586, 1910.
2. A Study of the Meyer Method of the Effect of Blood Serum and Certain Inorganic Salts on Surviving Arteries. Park, E. A., and Janeway, T. C., Proc. Soc. Exper. Biol. & Med. **9**: 51, 1911-1912.
3. A Criticism of Two Percussion Methods for the Diagnosis of the Enlarged Thymus. Park, E. A., and McGuire, W. C., Arch. Int. Med. **10**: 214, 1912.
4. Observations With Regard to the Action of Epinephrin on the Coronary Artery. Park, E. A., J. Exper. Med. **16**: 532, 1912.
5. The Question of Epinephrin in the Circulation and Its Relation to Blood Pressure. Park, E. A., and Janeway, T. C., J. Exper. Med. **16**: 541, 1912.
6. Physiological Action of Epinephrin on the Bronchi. Park, E. A., J. Exper. Med. **16**: 558, 1912.
7. Defective Development of the Right Lung, Due to Anomalous Development of the Right Pulmonary Artery and Vein, Accompanied by Dislocation of the Heart Simulating Dextrocardia. Park, E. A., Proc. New York Path. Soc. **12**: 88, 1912-1913.
8. An Infectious Endocarditis Following Measles in a Child Aged Two and One-half Years. Park, E. A., Proc. New York Path. Soc. **12**: 94, 1912-1913.
9. Thoracic Complications of Rickets. Howland, J., and Park, E. A., Am. J. Obst. **70**: 536, 1914.
10. Some Results in Thymus Extirpation. Howland, J., Park, E. A., and McClure, R. D., Am. J. Obst. **70**: 860, 1914.
11. The Effect of Thymus Extirpation. Howland, J., McClure, R. D., and Park, E. A., Proc. Am. Pediat. Soc. **26**: 274, 1914.
12. Review of the Literature of the Past Two Years on the Organs of Internal Secretion. Park, E. A., Am. J. Dis. Child. **12**: 477, 1916.
13. The Costochondral Junction in Rickets. Park, E. A., Tr. Am. Pediat. Soc. **28**: 130, 1916.
14. Extirpation of the Thymus in the Guinea Pig. Park, E. A., J. Exper. Med. **25**: 129, 1917.
15. Study of a Small Outbreak of Poliomyelitis in an Apartment House, Occurring in the Course of an Epidemic in a Large City. Burrows, M. T., and Park, E. A., Arch. Int. Med. **20**: 56, 1917.
16. Experiments on the Vasoconstrictor Action of Blood Serum. Janeway, T. C., Richardson, R. B., and Park, E. A., Arch. Int. Med. **21**: 565, 1918.
17. A Children's Dispensary Organized on the Basis of Appointments for Patients. Park, E. A., and co-workers, Modern Hospital **3**: No. 2, Aug., 1919.
18. The Results of Thymus Extirpation in the Dog. Park, E. A., and McClure, R. D., Am. J. Dis. Child. **18**: 317, 1919.
19. Memoires Originaux. Un Dispensaire de la Croix-Rouge Americaine en France. Park, E. A., Arch. de méd. d. enf. **22**: 393, 1919.
20. A Case of Hypersensitiveness to Cow's Milk. Park, E. A., Am. J. Dis. Child. **19**: 46, 1920.
21. Some Observations on Rickets. Howland, J., and Park, E. A., Proc. Am. Pediat. Soc., May, 1920.
22. Acrocephaly and Scaphocephaly With Symmetrically Distributed Malformations of the Extremities. A Study of the So-called "Acrocephalosyndactylism." Park, E. A., and Powers, G. F., Am. J. Dis. Child. **20**: 235, 1920.
23. The Dangers to Life of Severe Involvement of the Thorax in Rickets. Park, E. A., and Howland, J., Bull. Johns Hopkins Hosp. **32**: 101, 1921.
24. Studies on Experimental Rickets. I. The Production of Rachitis and Similar Diseases in the Rat by Deficient Diets. McCollum, E. V., Simmonds, N., Parsons, H. T., Shipley, P. G., and Park, E. A., J. Biol. Chem. **45**: 333, 1921.
25. Studies on Experimental Rickets. II. The Effect of Cod Liver Oil Administered to Rats With Experimental Rickets. Shipley, P. G., Park, E. A., McCollum, E. V., Simmonds, N., and Parsons, H. T.: J. Biol. Chem. **45**: 343, 1921.
26. Studies on Experimental Rickets. III. A Pathological Condition Bearing Fundamental Resemblances to Rickets of the Human Being Resulting From Diets Low in Phosphorus and Fat-Soluble A: The Phosphate Ion in Its Prevention. Shipley, P. G., Park, E. A., McCollum, E. V., and Simmonds, N., Bull. Johns Hopkins Hosp. **32**: 159, 1921.
27. Studies on Experimental Rickets. IV. Cod Liver Oil as Contrasted with Butter Fat in the Protection Against the Effects of Insufficient Calcium in the Diet. McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., Proc. Soc. Exper. Biol. & Med. **18**: 275, 1921.
28. Studies on Experimental Rickets. V. The Production of Rickets by Means of a Diet Faulty in Only Two Respects. Shipley, P. G., Park, E. A., McCollum, E. V., and Simmonds, N., Proc. Soc. Exper. Biol. & Med. **18**: 277, 1921.

29. Studies on Experimental Rickets. VI. The Effects on Growing Rats of a Diet Deficient in Calcium. McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., Am. J. Hyg. **1**: 492, 1921.

30. Studies on Experimental Rickets. VII. The Relative Effectiveness of Cod Liver Oil as Contrasted With Butter Fat for Protecting the Body Against Insufficient Calcium. Shipley, P. G., Park, E. A., McCollum, E. V., and Simmonds, N., Am. J. Hyg. **1**: 512, 1921.

31. Studies on Experimental Rickets. VIII. The Production of Rickets by Diets Low in Phosphorus and Fat-Soluble A. McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., J. Biol. Chem. **47**: 507, 1921.

32. II. The Prevention of the Development of Rickets in Rats by Sunlight. Shipley, P. G., Park, E. A., Powers, G. F., McCollum, E. V., and Simmonds, N., Proc. Soc. Exper. Biol. & Med. **19**: 43, 1921.

33. The Radiographic Evidence of the Influence of Cod Liver Oil in Rickets. Park, E. A., and Howland, J., Bull. Johns Hopkins Hosp. **32**: 341, 1921.

34. The Prevention of Rickets in the Rat By Means of Radiation With the Mercury Vapor Quartz Lamp. Powers, G. F., Park, E. A., Shipley, P. G., McCollum, E. V., and Simmonds, N., Proc. Soc. Exper. Biol. & Med. **19**: 120, 1921.

35. A Delicate Biological Test for Calcium-Depositing Substances. McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., Proc. Soc. Exper. Biol. & Med. **19**: 123, 1921.

36. The Effect of Diets Very High in Phosphorus and Very Low in Calcium on the Development of the Bones in Young Rats. Park, E. A., Shipley, P. G., McCollum, E. V., and Simmonds, N., Proc. Am. Soc. Biol. Chem. **16**: 7, 1921.

37. Is There a Substance Other Than Fat-Soluble Associated with Certain Fats Which Plays an Important Role in Bone Development? McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., Proc. Am. Soc. Biol. Chem. **16**: 6, 1921.

38. Studies on Experimental Rickets. X. Rickets and Rickets-like Diseases Produced in Rats by Deficient Diets. Shipley, P. G., Park, E. A., McCollum, E. V., and Simmonds, N., Dental Cosmos, March, 1922.

39. Studies on Experimental Rickets. XII. Is There a Substance Other Than Fat-Soluble Associated With Certain Fats Which Plays an Important Role in Bone Development? McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., J. Biol. Chem. **1**: 5, 1922.

40. Studies on Experimental Rickets. XIII. The Function of the Organic Factor as Exemplified by Cod Liver Oil. Shipley, P. G., Park, E. A., McCollum, E. V., and Simmonds, N., Tr. Am. Pediat. Soc., 33rd Session, Chicago, 1921.

41. Studies on Experimental Rickets. XIV. The Prevention of the Development of Rickets in Rats by Sunlight. Powers, G. F., Park, E. A., Shipley, P. G., and Simmonds, N., J.A.M.A. **78**: 159, 1922.

42. Studies on Experimental Rickets. XV. The Effect of Starvation on the Healing of Rickets. McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., Bull. Johns Hopkins Hosp. **33**: 31, 1922.

43. Is There More Than One Kind of Rickets? Park, E. A., Shipley, P. G., McCollum, E. V., and Simmonds, N., Proc. Soc. Exper. Biol. & Med. **19**: 148, 1922.

44. Is There More Than One Kind of Rickets? Shipley, P. G., Park, E. A., McCollum, E. V., and Simmonds, N., Am. J. Dis. Child. **23**: 91, 1922.

45. Studies on Experimental Rickets. XVI. A Delicate Biological Test for Calcium Depositing Substances. McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., J. Biol. Chem. **51**: 41, 1922.

46. Studies on Experimental Rickets. XVII. The Effects of Diets Deficient in Calcium and in Fat-Soluble A in Modifying the Histological Structure of the Bones. McCollum, E. V., Simmonds, N., Kinney, M., Shipley, P. G., and Park, E. A., Am. J. Hyg. **2**: 97, 1922.

47. Studies on Experimental Rickets. XIX. The Prevention of Rickets in the Rat by Means of Radiation With the Mercury Vapor Quartz Lamp. Powers, G. F., Park, E. A., Shipley, P. G., McCollum, E. V., and Simmonds, N., Bull. Johns Hopkins Hosp. **33**: 125, 1922.

48. Studies on Experimental Rickets. XX. The Effects of Strontium Administration on the Histological Structure of the Growing Bones. Shipley, P. G., Park, E. A., McCollum, E. V., Simmonds, N., and Kinney, E. M., Bull. Johns Hopkins Hosp. **33**: 216, 1922.

49. Studies on Experimental Rickets. XXII. Conditions Which Must Be Fulfilled in Preparing Animals for Testing the Anti-Rachitic Effect of Individual Foodstuffs. McCollum, E. V., Simmonds, N., Shipley, P. G., and Park, E. A., Bull. Johns Hopkins Hosp. **33**: 296, 1922.

50. The Appointment System in the New Haven Dispensary. Park, E. A., Modern Hospital **19**: 165, 1922.

51. Recent Discoveries Concerning Rickets Which Throw Light on Its Prevention and Treatment. Park, E. A., Tr. Vermont State Med. Soc., October, 1922.

52. Certain Factors Causing the Deposition of Lime Salts in Bone. Park, E. A., Dental Cosmos, February, 1923.

53. The Influence of Radiant Energy Upon the Development of Xerophthalmia in Rats: a Remarkable Demonstration of the Beneficial Influence of Sunlight and Out-of-Door Air Upon the Organism. Powers, G. F., Park, E. A., and Simmonds, N., J. Biol. Chem. 55: 575, 1923.

54. A Proof of the Regulatory Influence of Cod Liver Oil on Calcium and Phosphorus Metabolism. Park, E. A., Guy, R. A., and Powers, G. F., Am. J. Dis. Child. 26: 103, 1923.

55. Experimental Production of Rickets With Diets of Purified Food Substances. Osborne, T. B., Mendel, L. B., and Park, E. A., J. Biol. & Exper. Med. 21: 87, 1923.

56. The Etiology of Rickets. Park, E. A., Physiol. Rev. 3: 106, 1923.

57. Kidney Hypertrophy Produced by Diets Unusually Rich in Protein. Osborne, T. B., Mendel, L. B., Park, E. A., and Darrow, D., Proc. Soc. Exper. Biol. & Med. 20: 452, 1923.

58. Recent Advances in Infant Feeding. Park, E. A., Proc. State (Conn.) Med. Soc., 1924.

59. Newer Viewpoints in Infant Feeding. Park, E. A., Proc. State (Conn.) Med. Soc., 1924; New York State J. Med. 24: 921, 1924.

60. Littérature Anglo-Américaino. Park E. A., Rev. franç. de pédiat. 1: 109, 1925.

61. John Howland, M.D. (1873-1926). Park, E. A., Science 64: 80, 1926.

62. Physiological Effects of Diets Unusually Rich in Protein or Inorganic Salts. Osborne, T. B., Mendel, L. B., Park, E. A., and Winternitz, M. C., J. Biol. Chem. 71: 317, 1927.

63. Transverse Lines in X-ray Plates of the Long Bones of Children. Eliot, M. M., Souther, S. P., and Park, E. A., Bull. Johns Hopkins Hosp. 51: 364, 1927.

64. Revue de la Littérature Pédiatrique aux États-Unis. Park, E. A., Rev. franç. de pédiat. 5: 383, 1929.

65. Primary Tuberculous Infection in the Infant. Park, E. A., South. Med. & Surg. 91: 449, 1929.

66. Shadows Produced by Lead in the X-ray Pictures of the Growing Skeleton. Park, E. A., Jackson, D. A., and Kajdi, L., Am. J. Dis. Child. 41: 485, 1931.

67. Some Aspects of Rickets. The First Blackader Lecture. Park, E. A., Canad. M. A. J. 26: 3, 1932.

68. Rickets. Park, E. A., and Eliot, M. M., Cyclopedia of Medicine, Philadelphia, 1933, F. A. Davis Co.

69. X-ray Shadows in Growing Bones Produced by Lead, Their Characteristics, Cause, Anatomical Counterpart in the Bone and Differentiation. Park, E. A., Jackson, D., Goodwin, T. C., and Kajdi, L., J. Pediat. 3: 265, 1933.

70. Paul Galvin Shipley, M.D. (1888-1934). Park, E. A., Am. J. Dis. Child. 49: 280, 1935.

71. The Recognition of Scurvy With Especial Reference to the Early X-ray Changes. Park, E. A., Guild, H. G., Jackson, D., and Bond, M., Arch. Dis. Child. 10: 265, 1935.

72. Congenital Scurvy. Jackson, D., and Park, E. A., J. Pediat. 7: 741, 1935.

73. Methods, Results and Opportunities of Four Years' Liaison Between Pediatrics and Psychiatry. Park, E. A., Proc. Third Conference on Psychiatric Education, 1935.

74. A Child Psychiatric Clinic in a Pediatric Department. Park, E. A., Canad. M. A. J. 38: 74, 1938.

75. The Use of Vitamin D Preparations in the Prevention and Treatment of Disease. Park, E. A., J. A. M. A. 111: 1179, 1938.

76. Rickets. Eliot, M. M., and Park, E. A., Brennemann's Practice of Pediatrics, vol. 1, chap. 36, Hagerstown, Md., 1938, W. F. Prior Co., Inc.

77. The Irregular Extensions of the End of the Shaft in the X-ray Photography in Congenital Syphilis With Pertinent Observations. Park, E. A., and Jackson, D. A., J. Pediat. 13: 748, 1938.

78. Observations on the Pathology of Rickets With Particular Reference to the Changes at the Cartilage-Shaft Junctions of the Growing Bones. Park, E. A., The Harvey Lectures, Bull. New York Acad. Med. 15: 495, 1939.

79. Renal Rickets (Renal Dwarfism; Renal Infantilism; Renal Hyperparathyroidism; Renal Osteitis Fibrosa Cystica). Park, E. A., and Jackson, D. A., Cyclopedia of Medicine, Philadelphia, 1940, F. A. Davis Co.

80. Rickets. Park, E. A., and Eliot, M. M., Cyclopedia of Medicine, Philadelphia, 1940, F. A. Davis Co.

81. The Pharmacopeia and the Physician. The Therapy of Rickets. Park, E. A., J. A. M. A. 115: 370, 1940.

82. Diet of the Child. Park, E. A., Proc. Dental Centenary Celebration, March, 1940.

83. El Tratamiento del Raquitismo. Park, E. A., Rev. Assoc. méd. argent. 55: 60, 1941.

84. Kenneth D. Blackfan, M.D. (1883-1941). Park, E. A., Tr. A. Am. Physicians 57: 7, 1942.

85. Rickets. Eliot, M., and Park, E. A., Brennemann's Practice of Pediatrics, vol. 1, chap. 36, Hagerstown, Md., 1943, W. F. Prior Co., Inc.

86. Prevalence of Rickets in Children Between Two and Fourteen Years of Age. Follis, R. H., Jr., Jackson, D. A., Eliot, M. M., and Park, E. A., Am. J. Dis. Child. 66: 1, 1943.

87. Surgical Treatment of Experimental Coarctation (Atresia) of Aorta. Blalock, A., and Park, E. A., Ann. Surg. 119: 445, 1944.

88. Social Aspects of Medicine. Park, E. A., J. Pediat. 27: 202, 1945.

89. Rowland Godfrey Freeman (1859-1945). Park, E. A., Tr. A. Am. Physicians 59: 14, 1946.

90. Changing Medical Care in Our Changing National Life. Park, E. A., Bull. New York Acad. Med. 23: 673, 1947; J. Pediat. 31: 599, 1947.

91. The Pediatrician and the Public: Open Forum. Park, E. A., and Harper, P., Pediatrics 3: 854, 1949.

92. Some Observations on Bone Growth. Park, E. A., Washington Univ. M. Alumni Quart. 13: 112, 1950.

93. The Prevalence of Scurvy at Autopsy During the First Two Years of Age. Follis, R. H., Jr., Park, E. A., and Jackson, D., Bull. Johns Hopkins Hosp. 87: 569, 1950.

94. Acceptance of the Kober Medal Award. Park, E. A., Tr. A. Am. Physicians 63: 26, 1950.

95. Vitamin D Malnutrition and Rickets. Park, E. A., Clinical Nutrition, Norman Jolliffe, F. F. Tisdall, and Paul R. Cannon, eds. New York, 1950, Paul B. Hoeber, chap. 16, p. 449.

96. Some Observations on the Morphological Basis for the Roentgenographic Changes in Childhood Leukemia, Follis, R. H., Jr., and Park, E. A., Bull. Johns Hopkins Hosp. 12: 67, 1951.

97. Renal Rickets. Harrison, H. E., and Park, E. A., Cyclopedia of Medicine, Philadelphia, 1951, F. A. Davis Co.

98. The Preservation of the Ideal in a University Children's Clinic. Park, E. A., Canad. M. A. J. 66: 473, 1952.

99. John Howland Award Address. Park, E. A., Pediatrics 10: 82, 1952.

100. Some Observations on Bone Growth With Particular Respect to the Zones and Transverse Lines of Increased Density in the Metaphysis. Follis, R. H., Jr., and Park, E. A., Am. J. Roentgenol., 1952. (In Press.)

INFANT FEEDING IN COLONIAL AMERICA

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SOMETIME someone will write the history of American pediatrics, but not immediately, I hope, because it is much too soon to appraise properly many of the revolutionary changes of the past few decades. Only seventy-five years ago American pediatrics was just beginning to assert its independence, so all the great advances that have been made during Dr. Park's lifetime as student, author, and teacher will certainly comprise the major portion of this history. One of the most important and interesting chapters of this book will be the history of infant feeding—important because the reduction in infant mortality from gastrointestinal diseases has been the greatest of all advances in the field of medicine, and interesting because of the kaleidoscopic changes in methods and ideas that have influenced doctors from time to time. The present article is an attempt to assist that future historian by placing on record the earliest phase of infant feeding in this country, a record of those methods that were in common use when pediatric knowledge was entirely dependent on the research and writings of authors in other lands.

BREAST FEEDING

The prohibitive mortality that usually accompanied artificial feeding in seventeenth and eighteenth century England made breast feeding essential for the survival of the race, yet the technique of such an important custom was seldom mentioned by the early colonists in America. There is ample evidence that nearly all infants were brought up on the breast, but one may diligently search both printed and manuscript material without finding much pertinent information. In one of the best of the early diaries, Samuel Sewall recorded only very few details about the feeding of his first child during its first week of life; and even that comprehensive diarist, Ebenezer Parkman, father of seventeen breast-fed children, never mentioned how often they were fed a day, whether they were fed when they cried or according to a schedule, or any other details of what to him must have been a commonplace procedure. There exist, however, some rules concerning Negro slaves which, although exceptional because of the economic factors involved, were undoubtedly formulated by white plantation owners and therefore reflect, at least in part, the fundamentals of breast-feeding technique among Virginians of the middle eighteenth century:

> Sucklers are not required to leave their homes until sunrise, when they leave their children at the Children's house before going to the field. The period of suckling is twelve months. Their work lies always within half mile of the quarter. They are required to be cool before commencing to suckle—to wait fifteen minutes at least in summer, after reaching the children's house before nursing. . . . They are allowed forty-five minutes at each nursing to be with their children. They return three times a day until their children

are eight months old—in the middle of the forenoon, at noon, and in the middle of the afternoon; till the twelfth month but twice a day, missing at noon; during the twelfth month, at noon only. . . . The amount of work done by a suckler is about three-fifths of that done by a full hand, a little increased toward the last.[1]

Colonial newspapers occasionally printed detailed instructions on breast feeding, but most, if not all, of these articles were merely copied from foreign sources. The *New London Gazette* of October 19, 1770, carried an article entitled "Management of Infants From the Birth With Directions for Putting Them to Breast," which turns out to be a verbatim copy of the sixth chapter of Hugh Smith's *Letters to Married Women* (ed. 2, London, 1768). In sticky, syrupy language, Smith merely enlarged his fundamental thesis that "Art cannot produce a diet with such an affinity to animal blood, as to render it proper for the tender bowels of a new born child." A few years after the colonial period but still early enough to reflect colonial methods of spreading pediatric information, a Northampton newspaper carried a long, interesting abstract of a booklet written by the Italian, Baldini, in 1784. He said that when mothers were unable to suckle their infants "the milk of animals is preferable to that of another woman, or to any factitious food whatever," but when he also said that nursing mothers should under no circumstances "have any perfumed powders or pomatum about them," there must have been at least a few faint smiles on the weather-beaten faces of those hardy mothers of Pioneer Valley in western Massachusetts, many of whom had been reared according to the precepts of the Reverend Jonathan Edwards.

Most of the purely American observations on breast feeding chiefly concerned mothers, who had their difficulties even when their infants did tolerably well. Occasionally, when the mother was stricken with a fever, a cold, or some other sudden illness, the infant was sent away to be temporarily breast fed by a neighbor. But most mothers had to struggle along as best they could and occasionally despite serious difficulties. In the Winthrop correspondence there is a letter written by John Bishop of Stamford who desired medical aid for his month-old infant, with its thrush and diarrhea, and for his wife who apparently was suffering from a post-partum psychosis (1658).

The most frequently mentioned complaint of nursing mothers was soreness of the breasts soon after commencing to nurse their infants. Mrs. Ebenezer Parkman had considerable difficulty during June, 1745, October, 1755, and again during February, 1758; and her daughter-in-law suffered similarly in July, 1758. Among Parkman's miscellaneous papers is an apparently much appreciated "Receipt for Chapp'd Nipples" which he copied from the *London Magazine* for April, 1768; and Robert Agnew, a mercenary, quack apothecary, advertised in the July 23, 1772, issue of the *Virginia Gazette* that he had an extra-special salve "good for Suckling Women's Nipples." Much more incapacitating though still not serious were the numerous breast abscesses suffered by colonial mothers. Parkman recorded that his first wife, soon after the birth of her first child (1725) "had a very Sore Breast which broke Twice and was a very great Affliction"; his second wife had a breast

abscess in July, 1758, and again in February, 1761; and his daughter was afflicted likewise in August, 1759. Mrs. Tristam Gilman of North Yarmouth also had to have her breast abscess "opened y^{e} 2^{d} Time" (1772). These complications must have been even more common than diaries usually reveal for every now and then some itinerant, bombastic surgeon, such as Dr. William Rand of Essex Street, Boston, would advertise that his extraordinary and secret salve would hasten the rupture of an abscess in the breast (1760).

With an infant on the breast practically all of her reproductive life the colonial mother was entitled to a few complications if not to sheer physical exhaustion. Life would have been strenuous enough had she nothing else to do but bear and nurse her numerous babies, but off in a wilderness her other household chores were great indeed. One gets a glimpse of the daily domestic life of a nursing mother from a letter written August 7, 1711, by Timothy Edwards to his wife who was still nursing their youngest child, Jerusha, then fifteen months old. In telling his "dear and loving companion" about life on a military expedition he tenderly reminded her in postscript fashion of only the most important of her thousand motherly duties:

> I hope thou wilt take Special care of Jonathan y^{t} he dont Learn to be rude & naught &c. of w^{ch} thee & I have Lately Discoursed. I wouldnt have thee venture him to ride out into y^{e} woods with Tim.
>
> I hope God will help thee to be very carefull y^{t} no harm happen to y^{e} little Children by Scalding wort, whey, water, or by Standing too nigh to Tim when he is cutting wood: and prithee take what care thou canst about Mary's neck, which was too much neglected when I was at home, & Let her also sometimes read over what She hath Learnt in the Grammar y^{t} she Maynt Loose it: and Let a new rope be speedily put upon y^{e} well pole, if it be not done already: and Let Esther & Betty Take their powders as Soon as the Dog Days are Over, & if they dont help Esther, talk further with y^{e} Doct^{r}: about her for I wouldnt have her be neglected: Something also Should be done for Anne who as thou knowest is weakly: & Take Care of thy Self, and Dont Suckle little Jerusha too Long.[2]

WET NURSING

Although wet nursing was a well-established custom in Europe, it is difficult to find definite proof of its widespread use in seventeenth century America. Cotton Mather had a wet nurse during his infancy (1663-1664); and Samuel Sewall employed wet nurses for at least three of his newborn infants (1677, 1678, 1688). It appears to have been common practice to employ wet nurses for infants during the first week or two of life while the mother recovered from her "groaning" or lying-in. In case of puerperal fever or other serious illness, and, of course, when the mother died during childbirth, wet nursing was usually considered obligatory. A letter in the Wolcott correspondence (1702) shows how difficult it was to obtain a wet nurse when the mother was sick during a raging epidemic. In such instances, wet nurses who lived in the neighborhood were usually sick themselves and those who lived in surrounding towns were reluctant to go where the disease prevailed. There must have been thousands of instances when the mother, though anxious to do so, was unable to nurse her infant for want of sufficient milk. After being shipwrecked off the coast of Florida in 1696, Jonathan Dickinson made many notes in his journal[3]

concerning his wife and six-month-old infant who nearly perished for want of food. The infant survived only because of chance meetings with friendly, lactating squaws. Elizabeth Hanson, when captured by the Indians (1724), lost her milk, and despite feeding her infant on "broth of beaver's guts, or other guts" the child was reduced to "just skin and bones." After reaching Canada the infant recovered on an Indian formula of beaten walnuts, corn meal, and water.[4] "But if you have the Calamity of Dry Breasts; or your Health will not permit you to *Give suck;*" wrote Cotton Mather to the mothers of his time, "Entertain it with Submission to the will of God."

Wet nurses were sometimes employed when children had chronic illnesses even though the mothers may have had sufficient milk, because of the common belief that illnesses could be transmitted through the milk and that cures might follow a change in the supply. When five-month-old Mary Sewall, for example, was having as many as ten "convulsion fitts" daily, her father sent her to first one wet nurse then another in a desperate effort to obtain relief (1711-1712).

In England, wet nursing had already fallen into disrepute by the early seventeenth century. Packing their "squawling brats" off to wet nurses was a convenient habit of the Ladies of Quality, of Fashion, of Taste, of Distinction, and of What Not, particularly when they desired "to preserve their shapes and avoid a little trouble." One of the first to expose this fashion was the Countess of Lincoln, mother of Lady Arbella who came to America in the Winthrop fleet. In 1622 the good Countess, well beyond the age of childbearing herself, suddenly realized that she had not been a very good mother in farming her eighteen children out to strangers, so with the aid of her Bible and her ghost writer, the eminent Thomas Lodge, she had no difficulty in proving beyond question that all mothers should nurse their own children. Dr. Walter Harris, whose book was the standard text on children between 1689 and 1748, was more vehement in his denunciation of fabulously rich, lazy mothers as well as of unscrupulous wet nurses, and he attributed a good share of the high infant mortality of his time to the callous disregard of the needs of helpless infants.

In this country, where wet nursing was regarded with more respect, Cotton Mather nevertheless did not exactly recommend it. In his *Ornaments for the Daughters of Zion* (1692) and *Elizabeth in her Holy Retirement* (1710) he warned mothers not to paint their faces or to be unfaithful to their husbands. "One of the First Things to be done, is to Give up your *New-born Child* unto the Lord, in His Holy *Baptism.* Thus rescue the Child, from the *Great Red Dragon,* who is watching to devour it." Then, borrowing a thought from the Countess of Lincoln, he went on to say: "You will *Suckle your Infant your Self* if you can; Be not such an Ostrich as to Decline it, merely because you would be One of the *Careless Women, Living at Ease.* Of such we read, They are *Dead while they Live.*"

William Cadogan, physician to the Foundling Hospital in London, was the next to caution against the perils of wet nursing. His exceedingly

popular "Essay upon Nursing and the Management of Children" was first published anonymously in London in 1748, and subsequently went through at least ten editions. It must have had tremendous influence even in this country. Extracts from it appeared on the front pages of the *Pennsylvania Gazette* (March 21, 1749) and the *Independent Advertiser* (Boston, July 10, 1749). His tenth edition was reprinted in Boston in 1772; his fifth edition in Philadelphia in 1773; and he was still being quoted in American texts nearly one hundred years after his essay first appeared in print. Many of Cadogan's ideas, as well as a few of Stephen Hales', appeared in Ames' *Almanack* for 1762. One paragraph on a "Page for the Ladies" in this almanac reads:

> It is an Error in Judgment on the Part of the Mother, who, only for the Preservation of her Beauty, and fine Shape of Body, would put out her Infant to Nurse; since suddenly to dry up a full Breast of new Milk in a healthy Woman does such Violence to Nature, as greatly exposes the Mother to such Diseases as may marr her Beauty and Shape both . . . for the Infant to be deprived of that Aliment that was congenital to its Nature, and put to the Breast of a Nurse, who differs in Constitution from the Child's, as much as one Species differs from another—happy! thrice happy for many a poor Infant, in such Cases, if its Nurse had been a Goat, and not a Woman! The former feeds on the tender Browse, and drinks only at the cool Fountain, but the latter sometimes feeds foul, and drinks deeply of that Liquor, which can and often does kill the Infant at second Hand, from the Breast of the Nurse; . . . when so delicate a Machine as the Body of an Infant is (whose very Bones were lately a fluid Mass) I say, when such a delicate Thing from the Lap and Care of Nature, comes to be jounced on the hard knees, or handled with the rough Fingers of a cruel Nurse, or ignorant Mother; it is a Wonder that there are no more crooked Limbs, dislocated Joints, and Cripples from Infancy, than there are.

Warnings against wet nurses, though certainly more applicable to English experience, were nonetheless sometimes necessary in America. Early on the morning of February 28, 1696, the infant, Mehetable Mather, was found dead in her nurse's arms. "Alas" her father sorrowfully recorded "she was overlaid by the nurse." Similar terse notes on sudden death from "overlaying" by the wet nurse may be found in the diaries of the Reverend William Cooper (1729) and Benjamin Dolbeare (1742 and 1748).

Despite all warnings and some catastrophes wet nursing became increasingly common. During the eighteenth century breast milk was the most frequently advertised commodity in American newspapers. With all its faults wet nursing was thought to be so far superior to dry nursing, or artificial feeding, that in court cases involving foundlings, orphans, or illegitimate infants, wet nurses were supplied by the county, town, or parish:

> At a Courtt helld the 25th of September 1666 for the County of Somersett in the province of Maryland . . . Whereas John Cooper petitioned the Court that his servant Susanna Brayfield had a bastard childd & that she saith itt is John Griffiths childd &c. The Court being likewise informed that the childd & the Mother of the said childd laye dangerous sick, Itt was ordered by the Court & desired That Mr John Winder shoulld go to Susanna Brayfield for to take her testimony whose the childds Father is & to see whether the child be in want, iff soe to take care for the providing a Nurse for the childd.

As early as 1685 Boston selectmen found that "maintaining bastards & poor people when they are sicke, and nurses for them" were significant items in their annual budgets. In many

Virginia parishes[6] the annual fee allowed wet nurses for illegitimate children was 800 pounds of tobacco (ca. 1730); and in 1759 the Massachusetts General Court, alarmed by the increasing cost to various towns from "their being obliged to take Care of lewd women at the lying in with Bastard children," decided that towns could bind out those mothers as servants for five years to help defray expenses.

In London the wet nursing system directly contributed to crime. Desperately poor young women were known to have abandoned or even murdered their illegitimate infants in order to become wet nurses for the infants of the rich. The infanticide problem was therefore chiefly economic. Though the general population was disinterested in the moral degradation of gin-drinking young mothers, a few men, such as Jonas Hanway and William Hogarth, fearlessly exposed the revolting details of this unseemly aspect of London social life. In America the infanticide problem, though periodically recurring, was basically moral. There were class distinctions in this country but they were not so marked, for the poor were not as poor and the rich were not as rich as they were in London. The unwed mother, fully aware of the public censure that followed any violation of the moral code, sometimes took her chances on concealing the infant's birth, which was regarded as great a crime as infanticide itself. But towns were small and since everyone "watch'd o'er one another" the infanticide aspect of the wet nursing system never got out of hand. Besides, with an alert constabulary constantly on guard against possible candidates for unearned town support, visiting, unwed, pregnant women, even those very close to term, were unceremoniously hustled out of town; and even infants were also regarded as potential, undesirable inhabitants:

> Elizabeth Pickworth being present Sayes She belongs to Salem, & that she came from thence into this Town [Boston] the 1st day of April [1707] & that She hath put out her child to nurss in this Town, & that her Selfe doth nurss at Mr Benja Dyers in Boston. She is by the Select men warned to depart wth her child out of this Town.

Another nurse-child was "warned out" of Malden in 1767.

Many more details of wet nursing customs in America may be obtained from countless advertisements that appeared periodically in newspapers. The first (1706) is a typical example:

> Any person that wants to put a Child a Nursing on the Breast, may repair unto John Campbell, Post-Master of Boston, and know further.

These advertisements appeared only occasionally at first, say four or five times annually, but by the second half of the eighteenth century they were appearing in nearly every newspaper and sometimes two or three in a single issue. This frequency could be misleading, but even allowing for those that were repeated in consecutive issues, there were still enough to justify the conclusion that wet nursing was an accepted and very common practice.

As a rule, the modesty of both advertising parties was scrupulously respected for practically all advertisements were published anonymously. At first the postmaster was the broker, but beginning about 1722 and consistently after 1735 the printer assumed this function. Only very few gave any clue to the possible identity of the wet nurse. One lived "in one of Deacon Gibson's Tenements, close by his Dwell-

ing-House" (1746); and another lived "in Roxbury next to the first Meeting-House" (1754); but any more definite identification was seldom stated.

Since the wet nurse profited not only from the sale of her milk but also in obtaining a better home, it was generally the wet nurse who advertised, though later a significant proportion of the advertisements were inserted by the family of the child. The disrepute of London wet nurses reached an all-time low in the 1740's when it was discovered that such galactagogues as gin and rum could have deleterious effects on growing infants, and this disrepute was reflected in American newspapers thereafter, since most advertisements stressed the moral character of the nurse. One was a "careful motherly Woman," some were "good wholesome" wet nurses, others were "of good character," and still more could be "well recommended." There was one whose qualifications were exceptionally appealing:

> Any Person that wants a Wet Nurse in the House, may hear of a healthy young Woman (whose Husband is at Sea) with a good Breast of Milk, by enquiring of the Printer.
>
> —*Boston Evening Post.*
> Nov. 14, 1737.

The numerous advertisements indicating that Boston infants were generally sent to wet nurses in the country could be misleading for many reasons. Boston wet nurses could learn of jobs by word of mouth whereas country wet nurses usually had to rely on newspapers for their livelihood. Or, the number of wet nurses in Boston may have been very great and still not great enough to fill the demand. It is possible that lack of experienced midwives in the country may have resulted in a relatively larger proportion of infant deaths thereby producing a large supply of country wet nurses. At any rate, the custom of sending infants to the country was very common and seems to have depended mainly on the belief that infants would thrive better in the country air. This custom was well established in seventeenth century England; and it received some scientific support in the eighteenth century when Jonas Hanway, after comparing the infant survival rate of London parishes with that of country parishes, attributed the difference to beneficial qualities of the atmosphere. In this country Benjamin Rush found that moving infants afflicted with "cholera infantum" to the country was the best of all treatments at his command. "Bad air" became the accepted explanation for overcrowding and the spread of diseases from person to person. Though the slums of Boston, New York, and Philadelphia cannot be compared to the slums of London, these American cities, nevertheless, grew at the expense of public health. As early as 1652 Boston had laws against throwing garbage, carrion, dead cats and rats, tobacco stalks, "or any stinking thing" into the streets; and at the close of the eighteenth century Abigail Adams wrote pretty harsh accounts of the flies, filth, and stench of Philadelphia. Under such conditions the belief that infants would thrive better in the country air did not require much scientific proof.

Regardless of explanations, the fact remains that a great many Boston infants were sent to be wet-nursed in the country. Nurses frequently advertised that they lived two, seven, eight, or ten miles outside of Boston; and occasionally one finds references to par-

ticular towns. It is regrettable that Capt. Francis Goelet did not enlarge upon his interesting observation concerning Marblehead when he wrote in his journal in 1750: "This Place is Noted for Children and Noureches the most of any Place for its Bigness in North America, it's Said the Chief Cause is attributed to their feeding on Cods Heads, &c. which is their Principall Diett." Could the "&c" possibly include cod livers? Arlington also was a very popular place for wet-nursed infants. The vital records reveal the death of a "Nurse child from Boston, age 5 months" on August 19, 1755; another "Nurse child from Boston [died] at Walter Dickson's" on October 15, 1756; and ten similar entries were recorded between 1757 and 1783. Since these records concern deaths only, it seems reasonable to conclude that many other infants survived and that Arlington did a bustling wet nurse business. There are a few other Arlington records of Boston "nurse" children dying between two and four years of age, probably meaning children who had been sent originally to be wet-nursed and who remained there after being weaned, although "nurse child" was occasionally applied to an older child who had been placed in a foster home to board.

There are less numerous but definite records of professional wet nurses in Charlestown, Chelmsford, Dorchester, Gloucester, Medford, Milton, Newton, Roxbury, Sutton, Waltham, Weston, and Woburn. Not all of the infants came from Boston. In Weston, "Dyed a Nurse Child at Mr. Bond named Abr. son of Abr. Waters of Charlestown"; and in Arlington died on November 24, 1782 "A Nurse Infant from Medford." Incidentally, one of these advertisements reveals America's first acknowledged baby specialist:

> A Good Wet Nurse that lives in that part of Milton call'd the Blue Hills, and under the same Roof with a well known skilful Woman for weakly Children, would take a Child to Nurse. Inquire of the Printer.
>
> —*New England Weekly Journal.*
> April 26, 1737.

None of the above New England references does more than suggest that parents may have sent infants to wet nurses merely to avoid personal inconveniences, but Virginia records are more definite. Philip Fithian, tutor at Nomini Hall, entered in his diary on December 24, 1773:

> . . . The conversation at supper was on Nursing Children; I find it is common here for people of Fortune to have their young Children suckled by the Negroes! Dr Jones told us his first and only Child is now with such a Nurse; & Mrs Carter said that Wenches have suckled several of hers—Mrs Carter has had thirteen Children She told us to night and she has nine now living. . .[7]

As late as 1791, Stephen Girard, merchant prince of Philadelphia, placed his daughter, Mary, when she was four days old, "out to Nurse with John Hatcher's Wife, at 10s Per Week." The child died when she was five months old.[8]

Inasmuch as this custom of baby farming on Virginia plantations came directly from England where it was widely practiced it would have been unusual had it not been practiced also by New England upper classes, at least to a limited extent. One of the earliest New England records of probable baby farming out of town occurs in the *Dorchester Town Records* for June 13, 1681. It seems that the selectmen, having previously been obliged to support one or two Dorchester infants of

doubtful paternity, were taking no chances with a stranger, even one fairly well-to-do:

> The same day Joseph Weeks Came to the Select men and desiered libertie to take a nurst Child of one Mr Stevens of Boston, Answer was returned that though the man may be sufficient, yet becaus it may not be a presedent unto others he was ordered to appoint the man to give something under his hand to some one of the Select men to secure the towne.

Records of better-than-middle class New England families boarding their infants away from home are not hard to find. Samuel Sewall visited his four-month-old grandson, "little Henry at Nurse" in Brookline in 1720. Mary, child of Judge Benjamin Lynde, Jr., of Boston, caught chicken pox while living in Roxbury when she was five months old. As previously mentioned, the Reverend William Cooper (1729) and the pewterer, Benjamin Dolbeare (1743, 1748), both lost infants when they were boarding out at wet nurses' homes. Thomas, five-month-old "nurse child" of the Reverend Roger Price of Boston, died at Arlington on July 6, 1749; Dr. Quincy of Boston lost his fourteen-month-old child who was living in Arlington in 1764; and an "Infant child of John Choate, Esquire, [died] at Mr. Steele's" in Gloucester in 1778. All in all the evidence, while not positive, is certainly suggestive that baby farming was practiced in New England as well as in Virginia.

WEANING

Weaning was usually regarded as an important episode in an infant's life, since it could not be foretold whether or not a serious illness would occur during the process. Cotton Mather, when his daughter Elizabeth was being weaned, took the occasion to preach a sermon entitled, "A Soul as a Weaned Child"; and other diarists recorded the weaning of their children as seriously as they recorded births and deaths.

The day for weaning was frequently determined well in advance. "Your mother intends to set about weaning your [fourteen-month-old] sister Judith next week" wrote Samuel Sewall on March 4, 1703. Apparently there were no rigid rules for determining when to wean, and it seemed to depend somewhat on the child's age but more on the season of the year. Lionel Chalmers of South Carolina said that children were often weaned when nine or ten months old. Negro slaves in Viriginia were allowed to nurse their children twelve months, whereas New England children were usually nursed much longer. My series of weaning cases is too small to be statistically significant but when there were no complicating factors the average age appears to have been about seventeen months. Since most women had children at least every two years and frequently more often, it appears that a mother did not wean one child until the next was nearly ready to be born. When the child was afflicted with a chronic illness, weaning frequently took place ahead of schedule in the hope that it would be beneficial. Hull Sewall was weaned when ten months old (1685) and John Sewall when nine months old (1724), but only because each suffered from repeated convulsions. John Parkman was weaned when fourteen months old (1754) probably in an attempt to cure his so-called "rickets." As to be expected, children were also weaned

early when the mother or wet nurse was taken suddenly sick. One of Sewall's children was weaned "a few days before we intended" because the wet nurse had "an Ague in her Breast"; and two Parkman children were suddenly taken off the breast when the mother became too ill to nurse them. Young Sammy Parkman was weaned when only ten months old (1752) no doubt to get him out of the house so as not to disturb his father who was suffering severely from rheumatism at that time.

The season for weaning apparently made some difference, because seldom was a healthy child weaned in New England during July, August, or September, unless there was sickness in the house. Chalmers, after some bitter personal experiences, advised not weaning until October.

Though there are not many records of children suffering as the result of weaning, most parents appeared pleasantly surprised when all went well as though they had anticipated some serious illness or at least a spell of boisterous commotion. Hannah Hull was "through the favor of God" weaned without any trouble (1659); and Judith Sewall "gave very little Exercise after 3 or 4 nights. Then her cousin Mary Moodey could receive her without any noise."

Weaning was sometimes a gradual process, but usually it was abruptly undertaken without any conditioning of the child. In many cases the mother simply hustled out of town and left the father at home to enjoy the doubtful pleasure. The Reverend Joseph Green, after taking his wife to Wenham, returned home to Salem Village to take charge of the child who was being weaned (1703). Mrs. Parkman of Westborough on one occasion went to Marlborough, on another to Worcester, and on still another to visit her neighbor, Mrs. Martin. In many other cases, the mother stayed at home while the child was abruptly dispatched, usually to the grandparents or some other relative. Sewall merely sent one child to the grandmother's chamber in another part of the house. Parkman sent his son, Samuel, to be weaned "at tother house." There is an unintentional bit of humor in old grandfather Hempstead's diary:

June 7, 1733. . . Son & Daughter Minor Came & brot their Child & left itt hear to wean & went home again & I went with them & Lodged there.

It is not known how frequently children were kept on the breast for what now would be considered as excessively long periods, though two instances have been found which show that weaning was occasionally delayed for quite some time:

Rehoboth July 14, 1735. This Day the Rev. Mr. David Turner of this Place, joined in marriage, Mr. Samson Mason, A Batchelor in the 85th Year of his Age, to Mrs. Abigail Farriss, a Widow of about 45 Years old, both belonging here: She had then a sucking Child, upwards of three Years old; which 'tis thought she must wean upon this Occasion.

—*American Weekly Mercury.*
August 14, 1735.

The other case concerns Reuben Butterfield who was born in Tyngsboro in October, 1727. "He was a suckling child till into his ninth year, and grew to be broad-shouldered and of great strength. He was the champion athlete of his settlement, and could leap twelve feet." Reuben still holds this all-American record.

The technique of weaning must have been handed down from mother to

daughter by word of mouth. The earliest printed material bearing on this subject that I have seen was published by Lionel Chalmers of South Carolina in 1776:

> It seems a prevailing mistake, that children ought to be weaned when they are nine or ten months old, whether they be strong or weakly. For having most of their teeth still to cut, and being, oftentimes, much disordered thereby, it *then* becomes necessary to administer medicines which are not always agreeable to the taste; so that from *this* time, some of them are so suspicious of whatever is attempted to be given, that they will not suffer a cup or spoon to touch their lips. And thus I have known many of them to be lost, when the disease could not be soon removed; for they could not be made to suck again, though their lives might have been saved by it. It is therefore safest, not to wean infants before they have all or most of their teeth, that they may have somewhat to trust in case of sickness; for they will take the nipple when all other nourishment is refused. The above rules have been followed in my own family, and they were also recommended to others with success, who, as well as myself, had lost several children by too early weaning and adhering to the usual way of dieting them. And even were they ever so strong and healthy, they should never be weaned till the month of October, when the weather begins to be cool and bracing; for during the relaxing heat of the summer, they are very generally liable to diseases in this climate.

ARTIFICIAL FEEDING

So-called "dry nursing" must have been given an extensive trial in Europe long before America was settled, because its accompanying dangers appear to have been fully realized in this country in the seventeenth century. On January 23, 1649, Martha Lyon of Stamford wrote triumphantly: "my little daughter . . . now about halfe yeare old . . . is well in health through mercy and a thriving child for one bred up without the breast, as this hath been." In Charles County, Maryland, during 1658, it was learned that "liuci Stratton was brought to bed of a bastard and that She most unnaturally dried up her milke through which actione, the infants life mought have bin in danger." Marie Dode, twenty-one years old, swore that the father "Mr Arthur Turner came to desier her to nurs his child and this deponant answered Shee coold not for Shee thought she was with child her self but if hee woold have it drie nurst she woold doe her best endeavor for it whear upon the Sayd Turner answered that if this deponant coold bring it up by hand Lucie Stratton shoold." For her part in the affair the sheriff punished Lucy with thirty lashes.[9]

During the eighteenth century the mere fact that so many wet nurses were employed is fair proof that bringing infants up "by hand" was considered as a dangerous undertaking. Even though the idea probably came to him from British sources Nathaniel Ames said in his *Almanack* for 1762 that "Many Infants are sick, and many die with the unsuitable Aliment they receive by the Hand." Despite this, there must have been many instances of infants successfully raised without the breast although a single entry in the diary of Joseph Pease of Suffield (1764) is the only direct evidence that has so far been discovered.

There exists considerable indirect evidence that infants were frequently brought up on the bottle. Sucking, or suckling, bottles have not only been preserved but there are numerous references to them in the early records. "One sucking bottle" was mentioned in the inventory of the estate of Love Brewster of Duxbury (1650), and

many similar records may be found in the inventories of later seventeenth and early eighteenth century estates. It is possible that some of the bottles may have been used for weaning livestock. Some, however, were unquestionably made for infants inasmuch as they were frequently made by skillful artisans. "Suckling bottles" were made by Henry Shrimpton, pewterer of Boston, whose estate was inventoried in 1666. They were also made by John Baker, another Boston pewterer, previous to 1697. In the estate of Simon Edgell, a Philadelphia pewterer, thirty three sucking bottles were valued at three shillings apiece (1742); and in the estate of Thomas Byles, another Philadelphia pewterer, fifteen sucking bottles were valued at 3/6 apiece (1771).[10] Little Increase Mather's sucking bottle was probably made of silver:

> March 6, 1700. This morning, the Child [then eight months old] received almost a miraculous Deliverance from Choaking, by a Pin, which he suck'd out of the silver nipple of his Bottel, tho' wee know not how it came there.

Among the items comprising the Westover Plate, which was a part of the estate of William Byrd, 3rd, there was a sucking bottle valued at £1 (1769), which probably means that it also was made of silver.

Sucking bottles were imported into Boston in 1690 if not long before, and were sold by various retail merchants throughout the eighteenth century. Joseph and Daniel Waldo "at the Sign of the Eliphant" on King Street, Boston, sold everything from snuff boxes to coffin nails including sucking bottles (1748). William Ball of Philadelphia sold "sucking bottles for children" in 1755; and in 1756 Gilbert Deblois, "opposite the Town-Pump, in Cornhill," advertised sucking bottles among scores of other useful household articles. At Zabdiel Boylston's apothecary shop in Dock Square, Boston, one could buy "Nipple shells" in 1712. "Nipple Glasses, Ditto with Pipes" could be bought from William Clark in 1766; and "Letter'd Nipple Glasses, ditto with Pipes" could be bought from Philip Kast in 1771. "Nipple Shells and Breast Pipes" were still being advertised in the *Connecticut Courant* in 1794.

Dr. Still in his *History of Paediatrics* said that boat-shaped and globular vessels with spouts could be traced back to the third century, and the cow's horn to the thirteenth century. At various times in different countries feeding utensils were made of earthenware, glass, wood, pewter, and silver. Hugh Smith's milk-pot or "bubby-pot" became popular in England after 1774, and George Armstrong revived the use of the cow's horn in 1777. Very likely different types of feeding utensils were used in this country although nearly all written records refer only to pewter bottles.

Very little information has been found respecting the kind of fluid mixtures used in feeding bottles before the Revolution. Mary Carter of Virginia, during a coroner's inquest on a case of infanticide (1679), testified "That she saw her mother bring out water & sugar to ye fire side and offered it to ye [newborn] childe and it would not take it," but even had it lived the child would not have thrived on water and sugar for very long. Samuel Martin of Woodbury, Connecticut, said in 1736 that he had "lost two new Milch Cows, on which we had considerable dependence for the sup-

port of my family, & especially my Infants," probably referring to his two-month-old triplets, but one cannot be certain of this in view of his other ten children under seventeen years of age.

Was goat's milk used for infant feeding? "Shee-goats" were frequently mentioned in early seventeenth century records of Massachusetts Bay, Plymouth, Maryland, and Virginia colonies, and were brought over certainly before 1627. "A good MILCH GOAT [was] Wanted Immediately" in Boston in 1772, the "immediately" suggesting a desperately sick child. Yet I have been unable to find any definite references to goat's milk as an infant food.

Connecticut newspapers for July, 1767, printed detailed instructions for infant feeding which may have been English in origin or perhaps American and signed by "A Lady of Quality" merely for effect. One hour after birth, the infant was to be given "a little oil of sweet almond, a little juice of sea onion, with a little sugar candy" and nothing else for twenty-four hours. Starting on the second day the infant could have two different mixtures: (1) "some spoon meat of fine wheat flour, boiled," and (2) one-half pint of spring water, boiled with a pinch of aniseeds, to which was to be added a little "sweet biscuit" before allowing to cool. Starting at 5 A.M. the child was to be fed some wheat flour mixture and some biscuit water; at 9 or 10 A.M. more biscuit water; at 1 P.M. some wheat flour mixture; between then and bedtime two or three feedings of biscuit water. This "Lady of Quality" failed to say how many children she had raised on this routine.

A method of feeding devised in Waterbury, Connecticut, was unique, never having been used before or since:

> We hear from Waterbury, that a Woman of that Town, who in the fourth or fifth Month of her Pregnancy, was taken with a most violent Longing, to eat the flesh from her Husband's Arms—he indulged her in making several attempts; but her Teeth were not sufficient for her Purpose;—and her unaccountable Longing continued, until her Delivery, which was about three Weeks ago. The infant refusing the Breast, or any other Sustenance usually given Infants, it was offered the raw Flesh of a Fowl, cut fine, and dipt in the Fowl's Blood; on which it has fed heartily every Day since its Birth, and is the only Food the Child has taken, till a few Days since, when it eat a little milk, mixt with blood.
>
> —*Essex Gazette.* Sept. 4, 1770.

In view of the paucity of original American instructions for feeding infants "by hand" it may be assumed that most mothers followed English folk-customs or popular English medical books. Many English authors, notably the influential Cadogan, with an ingrained prejudice against boiled milk, strongly advocated feeding nothing but breast milk until the child was three to six months old. After that, but only in case of necessity, one could give "thin light broths with a little bread or rice boiled in them" alternating with "toasted bread and water boiled almost dry and then mixed with fresh milk, not boiled." Hugh Smith allowed, again only when absolutely necessary, "a little warm milk and water, with a small quantity of Lisbon sugar." (By the early nineteenth century some American authors were advocating a formula of two-thirds milk, one-third water, and a "moderate quantity of loaf sugar.") But Cadogan and other writers are

more revealing by what they were against rather than by what they were for. Nearly all of them condemned "paps, panadas, gruels, &c . . . generally enriched with sugar, spice, and sometimes a drop of wine," which indirectly proves that such foods were commonly used for infants in the first half year of life.

As for solid foods for older infants the facts are also scanty. The Reverend Israel Loring said (1750) that "the Nurse puts the meat first into her own Mouth and chews and feeds the Child with it." This attempt to spare the child by "tempering" its food was apparently in vogue for a very long time because it was frequently and severely condemned by early nineteenth century authors. Such authors are sometimes useful in throwing some light on colonial feeding practices inasmuch as no revolutionary innovations occurred between the colonial period and their time. They allowed what we would call a general soft diet, including meat, for a child as soon as it had acquired sufficient teeth. But these authors also are more revealing by what they were against rather than by what they were for. Charles Caldwell (1802) denounced "cherries, currants, g r e e n apples, pears, peaches, cucumbers and radishes," indirectly disclosing that all sorts of food were given to children between eight and twelve months old. That colonial mothers frequently offered a "free diet" and relied more on trial and error than on medical advice is somewhat confirmed by a letter from Mary Badger concerning her son, George. She wrote to her mother on December 29, 1784: ". . . you would be diverted to see him at eight months old tied in his chair at table eating fat pork & Indian Cake for his dinner."

It is appropriate to conclude this article by quoting the most original and informative of all American authors on infant feeding. Lionel Chalmers of South Carolina, conservative enough to remain under the spell of William Cadogan, was at the same time radical enough to introduce some new ideas. His closing remarks on "preposterous" methods of infant feeding are excellent examples of the ever-changing customs of mankind throughout the ages:

> It is of the utmost consequence to their welfare, that infants should early be taught to feed, lest they suffer when it becomes necessary to keep the breast from them, which happens more frequently than most people are aware. And as before weaning they seldom are troubled with any other sort of acrimony than an acid one, the best diet for them is broth of different strength, according to the age and condition of the child. *This* may be made with any kind of lean meat, excepting pork, in which a few tops of parsley, and some grains of black pepper should be boiled, more especially for those who are troubled with flatulency: but it were better not to thicken it at all, though a little salt may be added. On *this* they would willingly feed from the first, if their tastes had not been vitiated by the sugar which is commonly put in whatever is given them. But these sweetened slops, the flour with which their food is usually made, together with the breast milk, are the causes whence they suffer in a greater degree from acidity, than they would do were broth substituted in the place of every other nourishment, excepting the milk they suck. I do not however confine them altogether to the broth of flesh meats; but, by way of change, they are allowed the liquor of stewed *whitings*, or of any other fish that is not oily: of which young children are generally fond. And when they are eight or ten months old, their broth may be a little thickened with the crumb of bread; and the latter may likewise be mixed with either the clear gravy of roasted lean meat, finely minced, chicken or veal once in a day. Neither should a sip of

sweet wine (such as that of *Malaga* or *Canary*) or even of some distilled spirit well diluted with water, be denied them once or twice daily, more especially if they be weakly or much depressed by the heat of the weather. . . .

The preposterous manner of feeding infants with *pap*, and other such indigestible food nauseously sweetened, is highly censurable at all times. . . .

During the *summer* and *autumn*, sucking infants ought to be daily allowed a little spirituous drink oftener than once in this country. And experience proves, that no children thrive so well here as those who every day, sip either a small quantity of *Canary* or other sweet wine, mixt with an equal proportion of water; or a little *rum* well diluted, at all seasons, when nothing forbids; and they might be accustomed to this, from the time they are four or five months old.

REFERENCES

1. Blanton, Wyndham B.: Medicine in Virginia in the Eighteenth Century, Richmond, 1931, p. 176.
2. Winslow, Ola E.: Jonathan Edwards, New York, 1940, The Macmillan Co., p. 41.
3. Andrews, Evangeline W., and Andrews, Charles M., editors: Jonathan Dickinson's Journal or God's Protecting Providence, New Haven, Yale University Press, 1945, pp. 48, 55, 58.
4. Drake, Samuel G., editor: Indian Captivities, Boston, 1839, Antiquarian Bookstore and Institute, p. 121.
5. Maryland Archives, Baltimore, 1937, vol. LIV, p. 642.
6. Vestry Book of Stratton Major Parish, King and Queen County, Virginia, 1729-1783, Richmond, 1931, p. 13. Moore, J. S.: History of Henrico Parish and Old St. Johns Church, Richmond, 1904, p. 231.
7. Farish, Hunter D., editor: Journal and Letters of Philip Vickers Fithian, Williamsburg, 1945, Colonial Williamsburg, Inc., p. 52.
8. Packard, Francis R.: Some Account of the Pennsylvania Hospital, Philadelphia, 1938, The Engle Press, p. 49.
9. Maryland Archives, Baltimore, 1936, vol. LIII, pp. 28, 33.
10. Laughlin, Ledlie I.: Pewter in America, Boston, 1940, Houghton Mifflin Co., two volumes, *passim*.
11. Saltonstall Papers, Mss., Massachusetts Historical Society. Courtesy of Mr. Stephen Riley, Librarian.

The following manuscripts have been found very useful: Parkman diaries in the American Antiquarian Society; Wolcott letters, Israel Loring diary, and Joseph Pease diary in the Connecticut Historical Society; Samuel Martin's memorial in the Connecticut State Library; Winthrop papers in the Massachusetts Historical Society; and the Gilman diary in the Maine Historical Society.

The letters of Abigail Adams and the Hull diary have been published by the American Antiquarian Society; Joseph Green's diary by the Essex Institute; Mather and Sewall diaries by the Massachusetts Historical Society; and the Hempstead diary by the New London Historical Society. Many miscellaneous notes have been found in the following periodicals: Mayflower Descendant, New England Historical and Genealogical Register, Minutes of the Boston Selectmen, Virginia Magazine of History and Biography, and the Vital Records of various Massachusetts towns. I am particularly indebted to Mrs. Eva L. Butler for allowing me to consult her notes on colonial medicine.

RETENTION OF WATER AND ELECTROLYTE DURING RECOVERY IN A PATIENT WITH DIABETIC ACIDOSIS

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IT HAS long been recognized that severe diabetic acidosis cannot be effectively treated by insulin alone. In addition to ketosis and hyperglycemia, the final stage is dependent on losses of water and electrolyte leading to acidosis, diminished extracellular and plasma volumes, and losses of potassium from the cells. While a great deal of data define the role of changes in sodium and chloride concentrations in extracellular fluids and accumulation of organic acids in producing acidosis, these studies do not measure the exact magnitude of the deficits of Na, Cl, K, and water. Knowledge of the deficits of these ions is necessary to interpret the role of the losses of Na and K in the production of acidosis and the part played by potassium deficits in producing the reduction in serum potassium concentration during treatment. Because of the difficulty of obtaining complete studies of these factors, the following balance during recovery of a case of severe diabetic coma will be reported. The data and assumptions used for interpretation are similar to the studies of infantile diarrhea made possible by Edwards A. Park in 1945.[1]

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*During this study, Edward L. Pratt was Senior Fellow of the National Foundation for Infantile Paralysis, Inc.

The patient was a 10-year-old girl who had been previously well. The diabetes apparently started one month previously with polydypsia and polyphagia. Symptoms progressed with nocturia and lethargy appearing after three weeks. The patient lost considerable weight. Eighteen hours before admission she vomited her supper; the next morning she vomited twice, and was admitted shortly before noon.

At this time she had hyperpnea, and dehydration was quite marked. The blood pressure was 105/65. While she was somewhat restless and irrational at times, she responded to questions coherently when aroused.

The therapy for diabetic coma was carried out for five days as is indicated in the outline of the studies. Recovery was uneventful except for an episode of loss of consciousness lasting for about thirty minutes and commencing about ten hours after treatment had been initiated. Although she was receiving intravenous glucose at this time, additional 25 per cent glucose was injected before the blood sample was taken. While the episode was regarded as hypoglycemic, the high blood sugar does not establish this diagnosis though it does not exclude it.

All intakes were weighed and aliquots were analyzed for dried weight.

nitrogen, fat, and electrolyte. Carbohydrate was computed from dietary tables. The urine was collected over the period without catheterization. No stools were passed except a small one on the fifth day. This was not analyzed. The data may be considered essentially complete balances for water, N, Cl, Na, and K since the amounts of these elements localized in stools would be insignificant. However, the data cannot be considered to give the balances of Ca and P during the last two periods since the stools on a milk diet contain considerable amounts of these elements.

The intakes are given in Table II. The collections were divided into the following periods:

Period I lasted twenty-four hours during which all fluids were given by slow intravenous infusion. The fluids containing potassium were started about two hours after the onset of treatment. Total insulin was 100 units.

Period II lasted forty-eight hours during which a mixture of whole milk, Dextri-Maltose, NaCl, KCl, and sodium lactate was given. The caloric intake was about 1,200 per day. Total insulin was 88 units.

Period III lasted forty-eight hours during which a mixture of milk, sucrose, and eggs was taken, providing about 1,200 calories per day. Total insulin was 88 units.

Table I shows the serum analyses. The time indicates which specimens were taken at the onset and end of the balance periods. The second sample was taken during the episode of loss

TABLE I. SERUM CONCENTRATIONS PER LITER

TIME (HR.)	H_2O (GM.)	HCO_3 (mM)	Cl (mM)	Na (mM)	K (mM)	P (MG.)	GLUCOSE (MG.)
0	901	8.2	101	139	5.9		5,200
10	920	16.0	105	129	4.4	14	2.950
24	921	20.4	100	130	5.1	16	1,530
72	938	26.1	98	140		29	2,600
120	934	27.3	96	141	4.4	38	880

TABLE II. INTAKE AND URINE EXCRETION

	WEIGHT (GM.)	SOLIDS (GM.)	WATER (GM.)	CHO (GM.)	FAT (GM.)	N (GM.)	Cl (mM)	Na (mM)	K (mM)	P (mM)	Ca (mM)	BODY WEIGHT (KG.)
Urine	1,237	86	1,151	65		6.74	16.3	7.1	16.2	7.5	2.7	22.6
Intake	4,006	159	3,847	136			191.0	221.0	65.7	0.0	0.0	
Balance	2,769	73	2,696	71		−6.74	175.0	214.0	49.5	−7.5	−2.7	24.5
Urine	1,476	74	1,402	29		17.0	95.7	10.6	38.3	10.8	8.6	24.5
Intake	3,532	508	3,024	293	100	14.1	113.3	84.4	128.7	89.3	100.5	
Balance	2,056	434	1,622	264		−2.9	17.6	73.8	90.4	78.5	92.0	25.1
Urine	1,709	98	1,612	50		15.4	76.2	30.3	101.1	28.2	4.8	25.1
Intake	3,265	454	2,811	216	107	18.5	108.3	78.0	122.5	98.2	93.1	
Balance	1,556	356	1,199	166		3.1	32.1	47.7	21.4	70.0	88.3	25.2

of consciousness. The initial serum shows marked metabolic acidosis, hyperglycemia, and hemoconcentration. Although the concentration of sodium in serum was low after twenty-four hours, serum bicarbonate was almost normal. The last two samples are essentially normal. Partial recovery from acidosis is evident after ten hours. Although serum phosphorus concentration was not determined on the initial sample, the concentration of phosphorus had evidently decreased rapidly during the first hours of treatment. Only the last sample of blood showed a normal serum phosphorus concentration. Previous studies indicate that a decrease in potassium concentration similar to that of phosphorus would have occurred if K had not been administered early.

The intakes and urine contents are shown in Table II.

The evaporative water losses and the water balances were calculated as described by Peters and Van Slyke.[2] The evaporative losses were 855 during the first period and 1,381 and 1,396 in the last two periods. If 43 Gm. of water were evaporated for each 100 calories metabolized, the caloric expenditure was 2,000 during the first day and 1,600 during each day of the succeeding periods. The latter figure agrees well with the estimated heat production of a girl of her size. Owing to the overbreathing of acidosis, insensible water loss was probably high in relation to heat production during the first day. It should be noted that the evaporative water losses indicate that there could have been no significant sweating and hence skin electrolyte losses were minimal. In order to calculate water balances, caloric expenditure was assumed to be 1,800 on

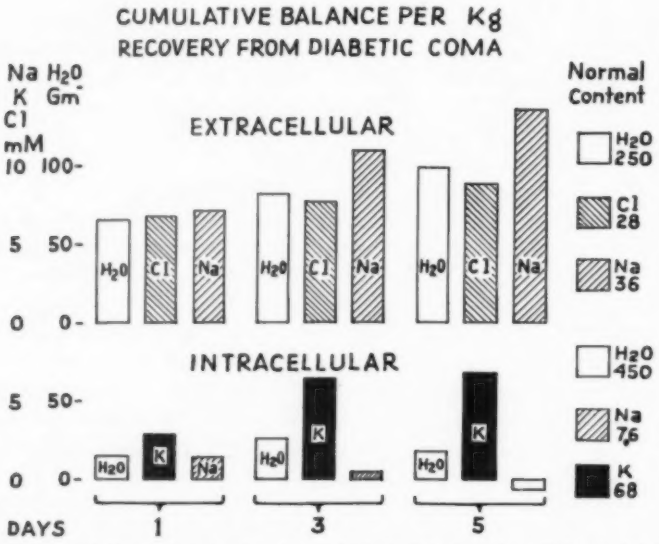

Fig. 1.—The cumulative balances of water and electrolyte in extracellular and intracellular fluids calculated per kilogram of body weight. For comparison, the estimated contents in 250 c.c. of an ultrafiltrate of plasma and 450 c.c. of intracellular water of muscle are shown.

the first day and 1,600 on the subsequent days. The water balances were 2.05, 0.63 and 0.19 kg. during the successive periods.

Using the assumption that the balance of chloride remains extracellular, the serum analyses and balances were used to calculate the probable distribution of the retained water and electrolytes.[1] The data were calculated back from a final assumed apparent volume of distribution of chloride of 25 per cent of the body weight. Previous studies indicate that extracellular volume remains normal or increases during starvation, so this high value in relation to body weight is justified and the balances probably indicate little excessive expansion of extracellular fluids. If the final chloride space is assumed to be 20 per cent of the body weight, the initial chloride space is only 11 per cent of the final weight—a figure which is too low to be credible. The results of these calculations are represented as accumulative balances of water and electrolyte in extracellular and intracellular fluids per kilogram of final body weight in Fig. 1.

The total retentions during five days were 114 Gm. of water, 9 meq. of Cl, 13.3 meq. of Na, and 6.1 meq. of K per kilogram of final weight. If a correction is applied for the loss of nitrogen, the deficit of K would be 6.9 meq. per kilogram of body weight. Part of this retention was used to form glycogen—probably about 1 meq. per kilogram. Thus the deficit of K was only moderate in this patient when compared to that demonstrated in some cases of diarrhea[3] or metabolic alkalosis.[4, 5]

The ratio of retained Na to Cl is 1.47, which is greater than the ratio in extracellular fluids and indicates a relative retention of Na over that necessary to form extracellular fluid of about 2 meq. per kg. The difference between the serum concentrations of Na and the sum of those of bicarbonate plus chloride in successive analyses of the serum indicate that the organic acids disappeared rapidly. The second serum analysis apparently represents the degree of acidosis dependent chiefly on the disturbed balances of Na, Cl, and K. This conclusion is likely because the intakes of Na and Cl were in the ratio found in interstitial fluid during the first day of treatment.

The over-all retentions give little evidence of excessive intracellular Na at the onset of treatment. Na apparently entered the cells in the first period when K deficits were still fairly large. This sodium left the cells as more potassium was retained.

DISCUSSION

In 1933 Atchley and associates[6] reported the intakes and outputs of electrolytes on withdrawing insulin and on restoring insulin to two patients with diabetes. The experiments were carried out only to the point just before the onset of severe symptoms of diabetic acidosis. Although the studies depended on estimation of sodium by difference, they agree with subsequent studies and demonstrate clearly the large losses of Na, Cl, and K before the final stage of diabetic coma. Potassium was lost in excess of nitrogen as indicated from the relation of K to N in the body. Similar observations were repeated recently by Butler and co-workers.[7] These authors found the decrease in weight to be 0.05 kg.; the

losses were 3.2 meq. of Na, 2.1 meq. of Cl, and 4 meq. of K per kilogram of body weight. They estimated that a final day of diminished fluid intake and vomiting would lead to the following losses: weight 0.11 kg.; Na, 5 meq.; Cl, 4 meq., and K, 6 meq. per kilogram of body weight. They found little evidence of loss of phosphorus in excess of nitrogen but because they did not estimate the Ca balance, significant losses of cellular phosphorus cannot be excluded.

Danowski and associates[8] estimated the retentions over three to four days of treatment in seven patients with diabetic coma. The data are essentially comparable to the present study except that physiologic saline was used to replace deficits of extracellular electrolyte. From 14 to 28 mM of NaCl per kilogram of body weight were given during the first day of treatment. When the larger amounts were given, the retentions after twenty-four hours were excessive, as was indicated by the subsequent excretion of Na and Cl and high concentrations of sodium and chloride in serum at this time. However, the final retentions of Na and Cl were usually 8 to 10 meq. per kilogram and usually in equivalent amounts. Twenty-five millimols of NaCl per kilogram of body weight were retained in one of the patients receiving about 28 mM of NaCl during the first day of treatment. This finding indicates that large amounts of NaCl are not readily excreted by some patients and the initial replacement of NaCl should be close to the estimated deficit, which is unlikely to be greater than 8 mM Cl and 12 mM Na per kilogram of body weight. From 4 to 6 meq. of potassium per kilogram of body weight were retained by most of their patients. The variations in their patients indicate that exact figures for the deficits of electrolyte cannot be estimated clinically for a particular case. However, the data from available studies are consistent with the following retentions in severe diabetic coma: water 100 to 125 Gm. per kilogram; Na, 6 to 12; Cl, 4 to 9, and K, 2 to 7 meq. per kilogram of body weight.

The data of Butler and associates and the present study indicate that Na and Cl are lost in about the proportions found in extracellular fluids. The data of Danowski and associates suggest that the deficits are in equivalent amounts. Since the first two studies involved treatment with solutions in which Na and Cl were given in the ratio found in interstitial fluid, and the last study only NaCl was given, the retentions found may depend over the periods of observation on the loads imposed by treatment. In any case, there is little evidence that diabetic acidosis is caused to a significant degree by deficits of Na relative to chloride greater than the respective amounts in normal extracellular fluids.

The implications of the balances on bicarbonate concentration may be illustrated in our patient. Since the ratio of Na and Cl administered during the first day was the same as that of extracellular fluids, the relative amounts in the body were altered after ten hours of treatment chiefly by the expansion of extracellular volume. At this time the difference between the sodium concentration in serum and the sum of the concentrations of HCO_3 and Cl had reached a value, indicating that substantially all ketones had been

oxidized. In other words, the acidosis at this time was chiefly dependent on the disturbance in body content of Cl, Na, and K. If this is true, the following equation calculates the deficit of Na available to form bicarbonate after extracellular volume has been restored.

$$(25\text{-}16)\ 0.25 = 2.25 \text{ meq. } NaHCO_3 \text{ per kg. of body weight}$$

(Deficit in bicarbonate concentration) (Extracellular water) = Na required in extracellular fluids.

The final balances indicate no significant disturbance in intracellular sodium at the onset of the study. However, a deficit of 6 meq. of potassium was present. If extracellular bicarbonate concentration was to be restored without replacement of potassium, about 4 meq. of Na would enter the cells. Hence about 6 meq. of Na in excess of Cl would be required to restore serum bicarbonate concentration if K deficit is not replaced. This calculation assumes replacement of extracellular fluids by solutions resembling interstitial fluids. During the initial replacement of extracellular fluids with a solution resembling interstitial fluid, about 2 meq. of Na lactate had been given. Hence the requirement of $NaHCO_3$ in excess of NaCl at the onset of treatment would be about 4.25 meq., but 8.25 might be required if the deficit of K in the cells was not replaced.

A frequently used method of calculating the dose of sodium bicarbonate in diabetic acidosis is as follows:

$$(25\text{-}CO_2)0.7 = \text{meq. } NaHCO_3 \text{ per kg.}$$

If the initial serum bicarbonate concentration is used, the amount of $NaHCO_3$ is 12 meq., and if the second concentration is used, 6 meq. per kilogram. In actual practice, physicians using this formula recommend consideration of the effect of accumulation of organic acids and only use about one-half the amount calculated from the initial bicarbonate concentration. However, it is obvious that the calculation is based on the false assumption that $NaHCO_3$ is distributed throughout all body water. Administration of the amount of $NaHCO_3$ which the formula prescribes has been shown to produce the predicted rise in the concentration of bicarbonate in serum fairly well in many cases. However, this result is dependent on the transfer of Na to the cells owing to deficits of this ion or potassium in the cells. The extent of these cellular deficits cannot be predicted precisely, and if they are not present, the full calculated dose of sodium bicarbonate is likely to produce alkalosis. Furthermore, the replacement of cellular deficits of potassium by sodium is undesirable since it tends to produce low concentrations of potassium in serum and extracellular alkalosis. There is no rational means of calculating a dose of sodium bicarbonate which will stabilize extracellular bicarbonate at normal levels until intracellular deficits are also restored.

The most rational justification for administration of $NaHCO_3$ is given by Guest.[9] He points out that insulin apparently does not act effectively as long as extracellular pH is greatly reduced. However, owing to the regulation of blood pH by respirations as well as bicarbonate concentration, relatively small increases in serum bicarbonate restore serum pH while enough $NaHCO_3$ to restore normal bicarbonate concentrations may lead to alkalosis in the early stages of recovery.[10] The

alkalosis results from persistent hyperpnea at a time when serum bicarbonate becomes normal, owing to rapid administration of large doses of $NaHCO_3$. For these reasons, the authors believe that the use of solutions containing Cl and Na in the ratio found in extracellular fluids provides enough Na in excess of Cl to increase serum pH and avoids the dangers of alkalosis. The order of magnitude of the deficits of Na and Cl suggests that 60 to 80 c.c. per kilogram of an isotonic solution containing Na and Cl in the ratio of interstitial fluid suffices to replace all deficits of Na and Cl, and little additional Na and Cl are needed for expenditure if ketosis is controlled. Additional fluid therapy need only provide water, chiefly as 5 per cent glucose, to cover water expenditure as urinary and insensible losses and potassium to prevent the development of low K concentration in the serum.

All studies indicate that while potassium concentration may be normal or slightly high at the onset of treatment, the concentration in serum decreases within the first two to ten hours and may reach levels leading to paralysis and electrocardiographic changes.[11] In normal subjects, insulin leads to decrease in serum potassium concentration but the effect is augmented in diabetic coma. When the circulation is disturbed owing to shock or the loss of water and extracellular electrolyte, potassium leaves the cells and sodium tends to replace the potassium deficits. This process is reversed by appropriate treatment. The magnitude of the decrease in serum potassium concentration during treatment of diabetic coma is dependent not only on the rapidity with which the defects of metabolism are corrected but also on the magnitude of the initial deficits of potassium. The therapeutic problem is, therefore, to prevent the decrease in potassium concentration which is likely to develop within four hours—at the time when insulin starts to work and extracellular volume is restored. Potassium may be started in two to four hours and if all fluids are given parenterally 2 mM per kilogram may safely be given during the next twelve to twenty-four hours. The abnormal losses will not continue if the ketosis and glycosuria are controlled. As soon as food can be taken, abundant potassium is available for replacement of cellular deficits. The indications for early administration of potassium in diabetic coma are quite clear but it is probably seldom necessary to continue potassium administration unless parenteral therapy is prolonged.

Butler,[7] Guest,[12] Franks[13] and their respective associates have recommended phosphate mixtures in diabetic coma. Chiefly on clinical grounds Franks and associates believed the results were thereby improved. They were able to raise serum phosphate concentration but serum phosphorus concentrations tended to become low soon after phosphate injections were stopped. Guest and associates[12] clearly demonstrated the change in red cell phosphate compounds, but it has not been demonstrated that the important phosphate compounds in other cells are similarly involved. Serum phosphate may almost disappear without symptoms attributable to this change. No symptom complex has been clearly associated with low serum

phosphate. On the other hand, certain patients collapse during treatment and die with complete paralysis which is not accompanied by low serum potassium and does not respond to K therapy. The importance of phosphate compounds in cellular metabolism makes further study of this problem important. The absence of obvious symptoms of paralysis in most cases of diabetic coma with low serum potassium should make one hesitate to conclude that low serum phosphate is without consequences in all patients. The present study does not permit an estimation of the deficits of cellular phosphate, although the probable losses of phosphate in stools indicate that cellular phosphate losses are unlikely to be large. However, exact estimations are needed and the balances must be corrected for Ca as well as nitrogen before retentions of phosphate can be attributed to cellular deficits.

SUMMARY

The retentions during recovery in a patient with severe diabetic acidosis were 114 Gm. of water, 9 meq. of chloride, 13 meq. of sodium, and 6 meq. of potassium per kilogram of body weight.

In the light of this and previous studies, the significance of losses of water and electrolytes was discussed. It is pointed out that the acidosis is due in large part to accumulation of organic acids and that the loss of Na in relation to chloride is little if any in excess of their ratio in extracellular fluids. The magnitude of the deficits of Na, Cl, and water indicate that about 80 c.c. per kilogram of a fluid containing Na and Cl in the ratio found in extracellular fluids suffices to replace most of the deficits of water and all the deficits of Na and Cl. As long as all fluids are given parenterally, provision for water without electrolyte in glucose solutions must be given to cover the obligatory expenditure of water in urine and as insensible loss. Although potassium deficits are moderate, the effects of insulin are likely to produce a rapid and dangerous decrease in serum potassium concentration. Potassium should therefore be administered as soon as insulin begins to reduce blood sugar (two to six hours). The amount to be given is apparently 2 to 4 meq. per kilogram during the first twenty-four hours.

REFERENCES

1. Darrow, D. C.: The Retentions of Electrolyte During Recovery From Severe Dehydration Due to Diarrhea, J. PEDIAT. **28**: 515, 1946.
2. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry Interpretations, ed. 2, vol. I, Baltimore, 1946, Williams & Wilkins Co., p. 14.
3. Darrow, D. C., Pratt, E. L., Flett, J., Jr., Gamble, A. H., and Wiese, H. F.: Disturbance in Water and Electrolyte in Infantile Diarrhea, Pediatrics **3**: 129, 1949.
4. Pearson, O. H., and Eliel, L. P.: Postoperative Alkalosis and Potassium Deficiency, New England J. Med. **243**: 471, 1950.
5. Darrow, D. C., Schwartz, R., Iannucci, J. F., and Coville, F. E.: The Relation of Serum Bicarbonate to Muscle Composition, J. Clin. Investigation **27**: 198, 1948.
6. Atchley, J. L., Loeb, R. F., Richards, D. W., Jr., Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidosis. A Detailed Study of the Electrolyte Balance Following the Withdrawal and Reestablishment of Insulin Therapy, J. Clin. Investigation **12**: 297, 1933.
7. Butler, A. M., Talbot, N. B., Burnett, C. H., Stanbury, J. B., and Maclachlan, E. A.: Metabolic Studies in Diabetic Coma, Tr. Am. A. Physicians **60**: 102, 1947.
8. Danowski, T. S., Peters, J. H., Rathbun, J. C., Quashnock, J. M., and Greenman, L.: Studies in Diabetic Acidosis and Coma, With Particular Emphasis on the Retention of Administered Potassium, J. Clin. Investigation **28**: 1, 1949.

9. Guest, G. M.: Diabetic Coma; Metabolic Derangements and Principles for Corrective Therapy, Am. J. Med. 7: 630, 1949.
10. Hartmann, A. F., and Erganian, J.: Treatment of Diabetic Acidosis, J. PEDIAT. 31: 274, 1947.
11. Holler, J. W.: Potassium Deficiency Occurring During Treatment of Diabetic Acidosis, J. A. M. A. 131: 1186, 1946.
12. Guest, G. N., and Rapoport, S.: Organic Acid-Soluble Phosphorus Compounds of the Blood, Physiol. Rev. 21: 410, 1941.
13. Franks, M., Ferris, R. F., Kaplan, N. O., and Meyers, G. B.: Metabolic Studies in Diabetic Acidosis. II. The Effect of Administration of Sodium Phosphate, Arch. Int. Med. 81: 42, 1948.

FACTORS ASSOCIATED WITH REDUCTION OF PREMATURE INFANT MORTALITY RATES IN THE UNITED STATES

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THE premature infant neonatal mortality rate has shown a downward trend in the past fourteen years (1935 to 1948) from 14.9 to 10.8 per 1,000 live births, a decrease of 28 per cent. It seems timely to analyze the factors that have influenced this favorable change and to consider steps that might be taken to bring about further reduction.

The major role that premature infant deaths play in the total infant mortality is apparent from nationwide vital statistics which became available after 1933 when the birth registration area included all states. It was found, in data for 1935, that one-third of the deaths under one year were reported as due to premature birth.*

Data on the trends of the premature infant neonatal mortality rates in this country during the period 1935 to 1944 with detailed analysis of the data for the year 1944 were published by the Children's Bureau in 1947.[1] In a later report, in 1950, the data were extended through 1948.[2]

The following facts were established for the United States as a whole: The largest percentage of premature infant deaths occur on the first day after birth; the death rate is higher among nonwhite than among white infants; and there is wide variation among the states in mortality from premature birth in the neonatal period (in 1948, the range was from a low rate of 7.7 per 1,000 live births in one state to a high of 16.2 in another, compared with the rate of 10.8 for the United States as a whole).

The trends of neonatal mortality from premature birth by age at death in the United States for the period 1935 to 1948 are shown in Fig. 1.[3]

It is clear that the greatest improvement in lowering these mortality rates has occurred among infants who survived the first week (age at death 7 to 29 days). Substantial progress has also been made in reducing mortality from premature birth on the first day, the period in which nearly two-thirds of the neonatal deaths occur. In contrast, the trend of the rates for premature infants in the age group 1 to 6 days declined slightly from 1935 to 1943, after which date it showed an upward trend so that the rate was nearly as high in 1948 as in 1935. Methods of care in this period need careful evaluation since the data presented suggest that more infants are now being saved on the first day to die in the period one day to one week.

It should be pointed out that the neonatal mortality rate from premature birth is based on those death certificates that state no other acceptable primary cause of death other than "premature birth," coded in accordance with the fifth revision of the International List of Causes of Death

*Here "premature birth" refers to deceased infants only and the term means a judgment reached by the physician certifying the cause of death.

(1938). In the sixth, and latest revision (1948),[4] certain changes were made which will provide more accurate information regarding the association of premature birth with various specified causes of neonatal deaths. Under the title, "Certain Diseases of Early Infancy," two new categories were added—*mention of immaturity* and *without mention of immaturity*—so that for 1949 and succeeding years it will be possible to obtain data in regard to the role that birth injury and some other conditions (but not congenital malformations) play in causing premature infant deaths. It should be emphasized, however, that the death rates after 1948 will not be comparable with previous data.

Other sources of information in regard to premature infants are state and city health departments which have published data in regard to mortality rates, incidence of premature births and additional special information available in some health departments from matched birth and death certificates. Nearly all of the states now include the items "birth weight" and "length of pregnancy" on their birth certificates. In many states, provision has been made on birth certificates for entry of such items as complications of pregnancy, labor, and

NEONATAL MORTALITY FROM PREMATURE BIRTH, BY AGE

United States, 1935-48

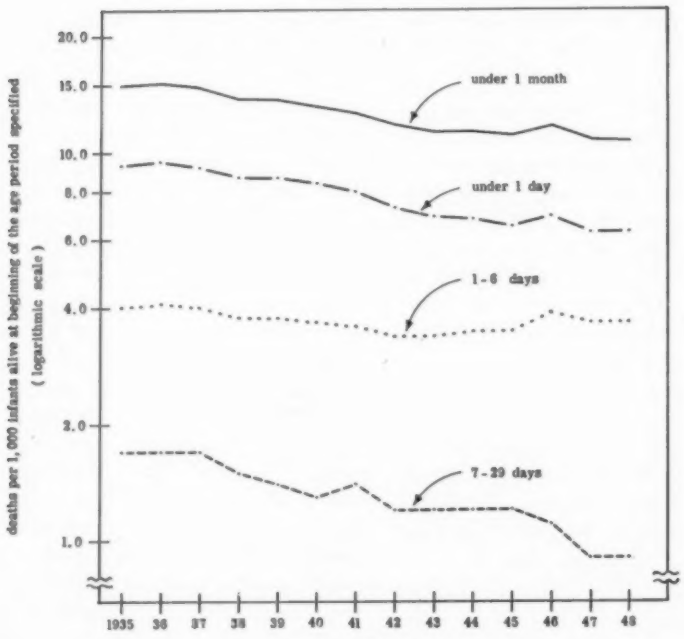

Fig. 1.

delivery with a view to obtaining information in regard to prenatal and natal factors associated with premature infant neonatal deaths.

Hospitals in different areas of the country have reported case fatality rates (deaths per 100 infants cared for) and detailed analyses of causes of death of these infants. The data on fatality rates are often difficult to interpret for a number of reasons, such as (1) differences in the definition of premature birth, (2) differences in inclusion of infants—some including all liveborn premature infants, others excluding certain infants as "nonviable" or for some other reason, (3) failure to separate data on the basis of (a) born in or born outside the hospital reporting, and (b) race, sex, single and plural birth, birth weight, economic status, and other factors indicated by the scope of the study.

A step forward in improving hospital reporting was taken when, recognizing the need for a definition of prematurity, the American Academy of Pediatrics[5] recommended in 1935 the following definition:

> A premature infant is one who weighs 2,500 gms. or less at birth (not on admission) regardless of the period of gestation. All liveborn premature infants should be included, evidence of life being heart beating or breathing.

The importance of compiling data in the birth weight groups now generally used was pointed out at this time, also. The definition of premature birth recommended by the World Health Organization[6] is now used in official National Vital Statistics for the United States.

> For the purpose of this classification an *immature infant* is a liveborn infant with a birth weight of 5½ pounds (2,500 grams) or less, or specified as immature. In some countries, however, this criterion will not be applicable. If weight is not specified, a liveborn infant with a period of gestation of less than 37 weeks or specified as "premature" may be considered as the equivalent of an immature infant for purposes of this classification.

Although data from hospitals on premature infant fatality rates from year to year are meager, it is certain that these rates have been reduced since the mortality rate for the United States has shown a marked decrease and according to latest available data about 90 per cent of births occur in hospitals. Moreover, the decrease in premature infant mortality rates has occurred while the percentage of births in hospitals has been increasing rapidly.

Fatality rates reported for each of the four birth weight groups show that the reduction in the total rate is due largely to reduced rates in the upper birth weight groups—1,501 to 2,000 and 2,001 to 2,500 grams. In the lower weight groups (0 to 1,000 and 1,001 to 1,500*) numbers of cases included in most reports are relatively few and vary from year to year so that the data are not statistically valid when presented on a yearly basis.

Levine,[7] however, has compiled the case fatality rates of 243 infants with birth weights under 1,000 grams and of 481 infants with birth weights 1,000 to 1,499 grams cared for in New York Hospital during a period of twelve years. When the cases were grouped in three four-year periods, the fatality rates in both groups show a downward trend. The decrease in the rate in the lowest weight group was 10 per cent; in the higher weight group, 35 per cent.

*Recommended birth weight groups.

The statistical data now available on a national and state basis as well as that from hospitals have contributed to reduction of premature infant deaths by drawing attention to the problems involved, pointing up areas of attack and assessing the results of steps taken to prevent these deaths.

In addition to statistical information available as to the problems involved in reducing premature infant mortality, there are certain general factors and certain specific factors that have influenced the decrease in the death rates.

The *general factors* are those that have influenced the decrease of 43 per cent in the total infant mortality rate in the same period in which the premature infant neonatal mortality rate has decreased 28 per cent. Among these factors are wider extension of general public health measures, improved obstetric and prenatal care, spread of maternal and child health programs by state health departments into rural as well as urban communities, correlation of welfare with health programs, increase in all types of basic research dealing with infants in the neonatal period, increased knowledge of methods for prevention and treatment of disease, and wider education of physicians and nurses and of the public in care of infants.

The *specific factors* that have influenced and are, at present, influencing the downward trend of premature infant mortality rates are numerous. It will not be possible, in the space permitted, to enumerate all of these and to give complete evidence for each of them in detail. It is, also, not possible to present them in chronological order since the evolution of various factors is not clear-cut and most of them are closely interrelated.

Among the factors that have played important roles are increasing recognition of the problems peculiar to prematurity; intensive research, clinical and laboratory, to determine the causes underlying pathology responsible for the high death rates; the improvement in methods for care; the development of educational programs for physicians, nurses and the public; and organization, on a state and local basis, of research and programs for improving care of premature infants.

Awareness of the magnitude of problems of prematurity has increased, so that, during the past fifteen or twenty years, interest in saving the lives of premature infants has developed from the individual physician's efforts to save the individual infant to *organized efforts,* not only in hospitals but in public health programs, state and local.

In the early 1930's, I made an informal survey of 105 hospitals in cities in various parts of this country to determine the status of premature infant care. In only four of them were fatality rates available and in the majority of them no special provisions had been made for the care of these infants. It is hardly necessary to point out the complete reversal of this situation that has ensued in the interval, so that at the present time there are relatively few hospitals that have not made provision for the specialized care of these infants.

During these same years advances have been made in *basic* as well as *specialized research* concerning the physiology and growth of premature infants as well as the causes, prevention, and treatment of the diseases to which they are specially susceptible.

Although data in regard to the causes of premature infant deaths are not available from official national statistics, studies have shown that the causes of the largest proportion of them are not determined. Among the known causes of death, congenital abnormalities, birth injuries, and infections were found by Potter[9] to be the next most frequent in the order given.

Since the information acquired by post-mortem examination has most value when correlated with clinical data this subject will be discussed in connection with methods for care.

Studies of the *special pathology* of the fetus and newborn infant were initiated in this country by Adair, who, with Potter, published the first book on this subject in 1940.[8] Potter[9] in a later report classified 44 per cent of neonatal deaths as due to "abnormal pulmonary ventilation" resulting from "immaturity of the tissues" and some of these to "hyaline membrane." These cases comprise, no doubt, a large proportion of the deaths of premature infants reported by others as "unknown." The "hyaline membrane" is found only in premature infants and in those who have breathed, but in spite of intensive research its significance is still not clear.

In regard to birth injuries the best methods for avoiding trauma to the premature infant during labor and delivery were first pointed out by Beck[10] in 1941. Pathologists have determined the most frequent sites for trauma and the association of the lesions with hemorrhage are well known. The causes and prevention of birth injuries and of congenital abnormalities have received and are receiving intensive study, as was evident at a conference of clinicians, pathologists, and other specialists held recently under the auspices of the New York Association for the Aid of Crippled Children.

The role that certain analgesics and anesthetics, given to the mother during labor and delivery, play in delayed respiration in the infant has been studied by Eastman, Taylor, and others, The information resulting from these studies is contributing to the reduction of premature infant neonatal deaths.

A tendency to *anoxia* has long been recognized as one of the handicaps of premature infants in the early period after birth. The need for increased oxygenation of the premature infant's blood has been demonstrated by the studies of Eastman[11] and more recently by Stewart Taylor and associates[12] and as a result its use for the more immature premature infants has become almost routine.

The best methods for resuscitation of infants who fail to breathe at birth are not clearly established, however. In many hospitals "mechanical resuscitators" are used but further clinical evaluation of the various types of resuscitators is needed and, even more, a study to develop specifications for their safety and efficiency.

The special susceptibility of premature infants to *infection* as one result of premature birth has long been known and the occurrence in hospitals of epidemics of impetigo, diarrhea, and respiratory tract infections formerly took a high toll of deaths from time to time. Such epidemics, judging from the gradual decrease in reports in the literature, are being gradually eliminated through preventive methods such as proper care of the skin, individualized techniques of care, limiting contact infection by restriction of traffic in nurseries, and adequate steriliza-

tion of feeding equipment and clothing. The cause of so-called "epidemic diarrhea" (nonbacterial) has not yet been determined, however. In a recent report fifteen full-term and six premature infants died in spite of intensive general therapeutic measures combined with the use of sulfonamides and antibiotics.[13]

Improvement in methods for premature infant care has been progressive. It was in 1922 that Hess established a hospital unit for the care of premature infants in the Sarah Morris Hospital, Chicago. In that year Hess[14] published the first book on premature infants, pointing out the extent of the problem, reviewing the sources of information, almost exclusively foreign, and setting forth the methods for care of these infants.

Since this time a vast amount of *research* bearing on all aspects of the problems of prematurity has been published so that many methods for care have a more secure basis and newer methods have been developed. Space does not permit the enumeration of more than a few examples, however.

Among these advances is the establishment of the premature infant's nutritional and fluid requirements largely through clinical and research studies by Levine, Gordon, and their co-workers. Since the reports of this series of studies are numerous, reference is made to one summary which appeared in THE JOURNAL OF PEDIATRICS in December, 1944.

Newer knowledge of the composition of body fluids and the fluid-electrolyte relationships is the basis for the present treatment of dehydration and acidosis.

Special techniques have been developed for administration of feedings to the most immature infants and for giving parenteral fluid and various types of therapeutic agents, particularly blood transfusions. Differentiation between the physiologic anemia of the neonatal period and the secondary anemia of later life has been made and the indications and appropriate methods for their prevention and treatment are now known.

The *environmental conditions* suitable to infants whose heat regulatory mechanisms are not well developed was reported by Blackfan and Yaglou in 1933.[15] These studies, conducted in air-conditioned nurseries, showed that different degrees of heat and relative humidity were required by infants of varying degrees of immaturity. The air-conditioned nursery has been gradually replaced by the nursery equipped with completely enclosed air-conditioned incubators. The advantages of this type of incubator are that isolation is provided in an environment with automatically controlled heat and relative humidity suitable to each infant and in which the oxygen concentration may be raised to the point considered desirable. Incubators should have the approval of the Underwriters Laboratories for use with oxygen. The safety and efficiency of incubators need to be studied again so that specifications, first published in 1940,[16] may be brought up to date.

The need for *standards for care* of premature infants became apparent as the numbers of premature infants cared for in hospitals increased. The Children's Bureau prepared the first Standards and Recommendations for Hospital Care of Newborn Infants—Full-term and Premature, which were approved by their Pediatric Advisory Committee and published in 1943.[17]

Many state and local health departments as well as hospitals then accepted these standards for care of premature infants. The American Academy of Pediatrics arranged with the Children's Bureau to take over this responsibility and published these Standards with some changes and additions in 1949.

To meet changing concepts of the best methods for care, a special committee of the Academy is now engaged in revising these Standards. There is special need to reassess and set up new standards for nursing care of premature infants.

Education and training in special methods for care of premature infants have gradually taken an important place in medical schools and hospitals as well as in public health programs. The demand by physicians and nurses for courses in this highly specialized aspect of care has increased so rapidly that it has taxed the resources of the relatively few available teaching centers. There are several teaching centers in which instruction and demonstration are carried out not only in the hospital, but integrated with the public health and welfare programs for prenatal care, health education, follow-up in the homes, and provision for meeting social and economic problems involved.

Recognition of the importance of *prevention of premature births,* particularly the earlier ones, with a view to reducing the deaths of premature infants has been relatively recent. This involves improvement in the quantity and quality of prenatal care with a view to reducing the incidence of complications of pregnancy, educating the mother in regard to a proper diet during pregnancy, and attending to the social and economic factors involved. Wallace[18] has found, in an analysis of data from birth certificates, New York City, 1951, that both the quantity and quality of prenatal care varied widely in the different districts and that in those districts having the highest incidence of premature births there was the lowest percentage of women receiving prenatal care.

The California State Health Department[19] has held, during the past May, two "working conferences" to identify the prevention of prematurity as "an entity in the public health program for maternal health." Recommendations were made in regard to organization of such programs by health departments, medical societies, hospitals, and other community agencies to this end.

Finally, *organization of premature infant care programs* has developed rapidly in the past fifteen years.

The first plan, city-wide in scope, came into effect in Chicago in 1934.[20] The program included provision of ambulance service to transport to hospital those infants needing such care, specialized public health nursing service, loan of heated beds, and a clinic for follow-up supervision of infants. In the period 1935 to 1940 the premature infant neonatal mortality rate among 12,187 infants showed a decrease of 41 per cent.[20] The services were gradually extended in the succeeding years and the rate for 1951 was 14.1 per 1,000 live births.[21]

State health departments have also developed programs for premature infant care in cooperation with physicians and hospitals. These programs were extended or initiated when funds were made available to the states, after the passage of the Social Security Act,

1935, to include them as part of the maternal and child health programs.[22]

As early as 1937, one state health department initiated an especially complete program directed by a staff pediatrician. Under a law passed that year, reporting of premature birth to the local board of health, transportation of the baby by the Department of Health to a hospital especially equipped for this care, and hospitalization were provided. Postgraduate training in pediatric and nursing care of premature infants was an integral part of this program. Another state health department that had one of the earliest and most comprehensive of the special programs provided hospital care for mothers threatened with premature delivery, as well as for care of premature infants. This same state as early as 1941 provided pediatric care, hospitalization and transportation for premature infants, and consultation and hospitalization for complicated obstetrical cases referred by obstetrical consultants. Training for nurses in the care of premature infants was offered under this plan also.

Within about five years after the passage of the Social Security Act over half the states made some provision in their plans for maternal and child-health services for special care of premature infants, or for improving the quality and availability of trained personnel to care for these infants. In the majority of these states emphasis was placed on one or more of the following: provision of incubators to local health departments, staff training through institutes, demonstrations, and graduate courses for physicians and nurses, pediatric consultation to hospitals and physicians, and in a few states special studies on the scope and nature of the prematurity problem.

During the 1940's the programs were enlarged in many states, particularly in the direction of encouraging and assisting the organization of centers for premature infant care in hospitals. These centers, which were appropriately equipped and staffed with medical and nursing personnel specially trained in management of premature infants, often served also as demonstration, educational and training centers for professional personnel in the state or from other states. Gradually, the areas within the states served by these centers have been extended, but statewide coverage is still exceptional. By 1951, three-fourths of the states provided some special measures for care of premature infants under their maternal and child health programs, either through education and training, or payment of hospital care, or public health nursing care, or in premature centers. Nineteen states had premature centers in operation either on a demonstration and nurse-training basis in a single hospital or in several hospitals which met standards for care of premature infants.

In addition, aid to states for hospital construction was made available under the terms of the Hill-Burton Law (The Hospital Survey and Construction Act) passed in 1946 and administered by the U. S. Public Health Service. One result was the construction of many new hospital units for premature infants. Plans for these units, submitted to the U. S. Public Health Service, were approved only if they met certain requirements based on Children's Bureau Standards for space and equipment.

SUMMARY

The trend of the premature infant neonatal mortality rate in the United States has shown a marked decline in the past thirteen years (1935 to 1948).

A review is made of some of the factors involved in the lowered death rate from prematurity.

Reference is made to the general measures that have influenced the decline in the total infant mortality as well as to certain specific factors that have influenced the decline in the premature infant mortality.

Specific factors are discussed, some examples of each of these are given, and areas for additional research into the problems of further reducing deaths from prematurity are indicated.

REFERENCES

1. Dunham, E. C.: Deaths of Premature Infants in the United States, Children's Bureau Statistical Series, No. 2, Washington, D. C., 1947, Federal Security Agency.
2. Mortality From Premature Birth and Associated Causes of Death (1948), Children's Bureau Statistical Series, No. 5, Washington, D. C., 1950, Federal Security Agency.
3. Analyses Prepared by the Children's Bureau from data supplied by the National Office of Vital Statistics, Public Health Service, Federal Security Agency, Washington, D. C.
4. The Effect of the Sixth Revision of the International Lists of Diseases and Causes of Death Upon Comparability of Mortality Trends, Vital Statistics—Special Reports, Vol. 36, No. 10, Dec. 3, 1951, Federal Security Agency, Public Health Service, National Office of Vital Statistics.
5. Proceedings, Fifth Annual Meeting of the American Academy of Pediatrics, June 7, 1935, Round Table Discussion on Prematurity, J. PEDIAT. 8: 104, 1936.
6. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, ed. 6, Vol. I, p. 212.
7. From data furnished by Prof. S. Z. Levine, Department of Pediatrics, New York Hospital, Cornell University Medical College, July 11, 1952.
8. Potter, E. L., and Adair, F. L.: Fetal and Neonatal Death, Chicago, 1940, University of Chicago Press.
9. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, 1952, Year Book Publishers.
10. Beck, A. C.: How Can the Obstetrician Aid in Reducing the Mortality of Prematurely Born Infants? Am. J. Obst. & Gynec. 42: 355, 1941.
11. Eastman, N. J.: Foetal Blood Studies. I. Oxygen Relationships of Umbilical Cord Blood at Birth, Bull. Johns Hopkins Hosp. 47: 221, 1930.
12. Taylor, E. S., Govan, C. D., and Scott, W. C.: Oxygen Saturation of the Blood of the Newborn as Affected by Maternal Anesthetic Agents, Am. J. Obst. & Gynec. 61: 840, 1951.

12a. Taylor, E. S., Scott, W. C., and Govan, C. D.: Studies of Blood Oxygen Saturation and Causes of Death of Premature Infants, Am. J. Obst. & Gynec. 62: 764, 1951.

13. Scott, R. B., Brown, G. P., and Kessler, A. D.: Diarrhea of the Newborn. Report of Epidemic and Results of Treatment with Streptomycin, Am. J. Dis. Child. 83: 192, 1952.
14. Hess, J. H.: Premature and Congenitally Diseased Infants, Philadelphia and New York, 1922, Lea & Febiger.
15. Blackfan, K. D., and Yaglou, C. P.: The Premature Infant: A Study of the Effects of Atmospheric Conditions on Growth and Development, Am. J. Dis. Child. 46: 1175, 1933.
16. Dunham, E. C., Dickenson, H. C., Gowans, G. J., and Witters, J.: Specifications for Incubators, Am. J. Pub. Health 30: 1415, 1940.
17. Standards and Recommendations for the Hospital Care of Newborn Infants—Full-term and Premature, Children's Bureau, Pub. 292, Federal Security Agency, 1943.
18. Wallace, H. M.: The Public Health Aspects of the Prevention of Prematurity, From the Bureau for Handicapped Children, New York City Department of Health and the Department of Pediatrics, New York Medical College and the Flower-Fifth Avenue Hospitals, presented at the Scientific Conference of the Association for the Aid of Crippled Children, New York, June 5-6, 1952.
19. The Role of the Health Department in the Prevention of Prematurity. California's Health, State Department of Public Health 9: No. 4, June 30, 1952.
20. Hess, J. H., and Lundeen, E. C.: The Premature Infant. Its Medical and Nursing Care, Philadelphia, 1941, J. B. Lippincott Co.
21. Personal communication from Herman N. Bundesen, M.D., President, Chicago Board of Health, Sept. 18, 1952.
22. From information furnished by the Children's Bureau, Social Security Administration, Federal Security Agency, Washington, D. C.

DEFORMITY OF VERTEBRAL BODIES IN CRETINISM

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THE "sabot shape" of upper lumbar vertebral bodies in gargoylism (Hunter-Hurler syndrome) is well known. Rather similar anomalies may be found in cretinism, but they have received little notice. One case was described in 1936,[9, 10] and the patient's subsequent progress is indicated in this paper (Case 1). Ellis[6] referred to this child and said that he had seen the deformity in "two typical cretins whose general condition and mentality responded well to thyroid treatment." In the second edition of his book Caffey[2] illustrated a case. Fairbank[11] wrote: "We have seen the typical spine of gargoylism in two cretins," and described one. Thomsen and Vesterdal[31] noted the similarity between changes sometimes seen in congenital hypothyroidism and Hurler's syndrome, and published an illustrative plate. Engeset, Imerslud, and Blystad[8] published a similar picture, which is not described in the text, although in the caption they comment: "Perhaps this finding may be seen in cases of hypothyreosis if we look for it."

ABRIDGED CASE REPORTS

CASE 1.—This child has been described previously.[9, 10] She was then 1 year 9 months of age. She was followed for a further six years. On 380 mg. thyroid daily she was unmanageable but she tolerated 320 mg., and responded partially to it, although she remained moderately stunted in growth and still looked cretinous. The kyphosis was unaffected and she developed epiphyseal dysgenesis in the hips; at 7 years only three carpal bones were ossified. She appeared to be a slightly atypical example of cretinism, responding incompletely to thyroid treatment.

CASE 2.—The history of this girl was typical of cretinism. The diagnosis was made when she was brought to hospital at 1½ years of age. The clinical condition, anemia, and hypercholesterolemia responded to thyroid treatment, but not satisfactorily, and she did not tolerate more than 64 to 96 mg. thyroid daily.

Radiography of the spine before treatment showed the eleventh thoracic vertebra poised above the twelfth, apparently ready to compress it, and there was a slight hook-deformity of the second lumbar (Fig. 1). At 2 years of age the femoral heads were still invisible, but two carpal centers had appeared, and there was marked upper lumbar kyphosis with hypoplasia of the body of the twelfth thoracic vertebra (Fig. 2).

CASE 3.—This boy, whose parents (unlike the others in this series) were cousins, was brought to hospital at 2 years of age, and diagnosed as "cretin but not complete." At 2½ years kyphosis was noticed, and the second lumbar vertebra was seen to be misshaped (Fig. 3). Stopping and restarting thyroid treatment were followed by the expected results on two occasions. At 7 years the weight and height were normal and the spine was hardly abnormal (Fig. 4), but the patient's intelligence quotient was 55 on the Stanford-Binet scale. At 8, 9,

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Fig. 1.

Fig. 2.

Fig. 1 (Case 2).—At 1½ years the eleventh thoracic vertebra is poised above the twelfth, which is displaced backward. The second, and to a less extent, the third, lumbar vertebrae are deformed.

Fig. 2 (Case 2).—At 2½ years the twelfth thoracic body is small, but the second and third lumbar vertebrae are only slightly deformed.

Fig. 3.

Fig. 4.

Fig. 3 (Case 3).—At 2½ years the second lumbar vertebra has a shelflike projection.
Fig. 4 (Case 3).—At 7 years the vertebra is nearly normal.

and 10 years, the blood cholesterol and electrocardiogram were normal, but the bone age was half what it should have been. This again was a rather atypical cretin, who tolerated only 48 mg. thyroid daily and responded partially. The spine became normal but the carpus did not, an experience which may be contrasted with that of Caffey[2] in which the spine remained abnormal although response was otherwise adequate.

thyroid and stopped giving it; then they brought him to London. He seemed to be a typical cretin except that the long dorsal curvature and lumbar lordosis, with flexion of the hips and knees, suggested mild Morquio's disease (Figs. 5 and 6). However, x-rays of carpus and hips, blood count, serum cholesterol, psychometry, and response to thyroid allowed no diagnosis but cretinism. He was treated with 112 mg. thyroid daily,

Fig. 5.

Fig. 6.

Fig. 5 (Case 4).—At 2 years there is a rounded kyphos more like that seen in mild Morquio's disease than in cretinism.

Fig. 6 (Case 4).—The radiograph shows a hypoplastic first and a slightly deformed second lumbar vertebra.

CASE 4.—This boy was seen to have spinal curvature at 6 months of age. At 1 year an x-ray of the spine showed no bony change but he was treated in plaster and then a spinal brace for ten months. An experienced pediatrician who saw him then noted only hypotonia and kyphosis; a year later he diagnosed cretinism. The parents were not satisfied by the response to

and at 5 years of age appeared to be a normal child except that the body of the first lumbar vertebra, although much larger, was still deformed (Fig. 7). The lateral radiograph showed a curious peg on the anterior aspect of the affected vertebra, the outline being reminiscent of the appearances of vertebrae in hypertrophic achondroplasia illustrated by Caffey.

Fig. 7 (Case 4).—At 5 years the first lumbar vertebra has grown although it is not yet normal.

Since the above paragraph was written, yet another case has been encountered (Case 13). This was an obvious but previously undiagnosed example of hypothyroidism in a girl aged 4½ years, in whom developmental retardation had been observed from early infancy. Although there had been no treatment, and there was at this late age no kyphosis. the second lumbar vertebra had a pronounced spike in the position of the peg in Fig. 7.

CASE 5.—This girl, first seen at 20 months of age and followed to 5 years, was in every way a typical cretin with a complete response to thyroid (on an average, 112 mg. daily). At 2 years there was slight kyphosis with reduction in size of the first lumbar vertebral body and deformity of the second (Fig. 8). They were normal at 5 years.

Fig. 8.

Fig. 9.

Fig. 8 (Case 5).—At 2 years there is hypoplasia of the first and deformity of the second lumbar vertebrae.

Fig. 9 (Case 12).—At 4½ years the spine is reported to be normal but there is some deformity of the second, third, and fourth lumbar vertebral bodies.

These six cases showed gross abnormalities of lumbar vertebrae, but not all cretins have them as the following cases show.

CASE 6.—This patient, a typical severe cretin, had kyphosis at 10 weeks of age but no bony abnormality showed on x-ray. At 9 months the spine is clinically and radiologically normal.

CASES 7 to 11.—In these typical cretins there was slight backward tilting of second and third or third and fourth lumbar vertebral bodies but of such slight degree that they were not considered abnormal.

CASE 12.—This girl was untreated until the age of 4½ years, when she had epiphyseal dysgenesis. The spine was abnormal (Fig. 9) but there was no kyphosis, a state of affairs similar to that in Case 13 (above), who reached the same age without treatment.

DISCUSSION

Deformity of the vertebral bodies in hypothyroidism appears to develop in postnatal life. In Case 2 there was kyphosis with a slight radiological change at 1½ years; kyphosis increased in the next six months. In Case 3 there was no kyphos at 2 years, but x-ray changes and kyphosis were seen at 2½ years. In Case 4, the parents noticed kyphosis at 6 months but there was no radiological change at 11 months, although it was obvious at 2 years. In Case 5 kyphosis was not noticed at 1 year 8 months, but a radiograph showed changes at 2 years.

In some patients the deformity diminished with thyroid treatment. In Case 4 there was improvement between the ages of 2 and 5 years; in Case 5 the deformity disappeared between 2 and 5 years; in Case 3 the spine became normal between 2½ and 7 years. Orthopedic treatment (extension in a plaster bed for six months) was given in Cases 2 and 4, and was followed by improvement. In two cases (12 and 13) diagnosed in the fifth year the vertebral bodies were abnormal but there was no kyphosis, although neither had been treated.

Generally it may be concluded that the abnormality of the spine is not a congenital deformity, that kyphosis develops between the ages of 6 months and about 2 years, that it is followed by radiological deformity, and that improvement may occur. Restitution to normal occurred in two patients, only one of whom had been treated orthopedically.

The development of kyphosis after birth, with the subsequent detection of spinal abnormality, is also seen in *gargoylism*. In this condition the spinal curve is often noted early, at from 3 to 6 months (Hurler,[15] Case 4 of Henderson,[13] Cases 3, 4, 5, and 10 of Lindsay and associates[22]). Radiographic abnormality has been found at 8 months (Case 5 of Ellis and coworkers[7]) and at 10 months (personal observation). The more rounded kyphosis of *Morquio's disease* develops later, usually after the first birthday.[3, 5, 23, 24] (The patients of Ruggles[28] and Davis and Currier[4] were probably examples of gargoylism and not of Morquio's disease.) Wheeldon[32] described vertebral wedging in *achondroplasia* but one of his patients was later found to have Morquio's disease.[26] Smith[29] also described it in achondroplasia. In a personal case the second and third lumbar vertebrae became deformed between the ages of 1 and 1½ years. Dr. L. G. Scott recently showed me pictures of a similar case in which the abnormality appeared at 9 months.

The pathology of Morquio's disease is virtually unknown, despite an instructive biopsy in one case.[5] The pathology of skeletal structures in gargoylism, achondroplasia, and cretinism has been studied by Lindsay and associates,[22] Strauss,[30] Knaggs,[19, 20] Harris and Russell,[12] and others. The changes are not, of course, identical, but in all there is deficient bone formation at the epiphyseal line, where a "boundary bone lamella" appears, and disorderly arrangement of cartilage columns, with degeneration of cartilage. These diseases are all chondrodystrophies, although to see them solely as such would necessitate a narrow view.

Harris and Russell[12] considered that there were three fundamental processes in bone growth; proliferation in cartilage, calcification in cartilage, and actual bone formation.

Bone formation depends on osteoblasts. These cells are deficient or abnormal in the chondrodystrophies we are discussing, but this alone cannot be essential for the production of wedge vertebrae, for it does not occur in osteogenesis imperfecta, the classical example of osteoblast deficiency, in which cartilaginous ossification is normal up to the final stage.[18]

The second process, calcification in cartilage, is defective in rickets, where vertebral bodies may be flattened but wedging is not seen. Its absence is surprising, for the importance of the mechanical factor in producing structural deformity of rachitic trabeculae has been shown in the most convincing manner by Dr. Park.[25]

Proliferation of cartilage is irregular and often deficient in cretinism, gargoylism, and achondroplasia, and is probably the essential abnormality which permits the formation of these dysplastic vertebrae.

As we have seen, the abnormality is uncommon in achondroplasia, and is not often noticed in cretinism. It is not constant in gargoylism (e.g., Hunter,[14] Jewesbury and Spence,[17] Ashby and collaborators,[1] Kressler and Aegerter,[21] and Jackson[16]). There must be some factor besides disturbed cartilage growth, and it is probably mechanical. In Fig. 1 the eleventh dorsal vertebra is poised dangerously above the hardly abnormal twelfth, which a year later shows the effect although it is small r a t h e r than wedged (Fig. 2). Most fractures of vertebral bodies occur in the twelfth dorsal and first and second lumbar vertebrae,[27] and it is these which are mainly affected in cretinism and gargoylism. The spine of the fetus is flexed, but the infant also spends much of his time curved in his mother's arm, and first sits with a bent back. The main stress falls on these particular vertebrae, and if they are softened by disease they are liable to a flexion deformity.

SUMMARY

1. Of thirteen cretins, one had a normal spine, five had minor abnormalities, and seven showed deformity of the bodies of the twelfth thoracic or first or second lumbar vertebrae. (The high incidence of abnormality is due partly to a special interest in the subject, which was responsible for the inclusion of two abnormal cases.)

2. Kyphosis with subsequent bony abnormality developed between the ages of 6 months and 2½ years. Bony abnormality without kyphosis was seen in two hitherto undiagnosed cases examined at 4½ years.

3. The deformity may disappear under treatment with thyroid.

4. Similar deformities are seen in other diseases in which there is chondrodystrophy.

5. The affected vertebrae are those most subject to trauma, and the abnormality is probably caused by the stress of flexion acting on chondrodystrophic vertebral bodies.

REFERENCES

1. Ashby, W. R., Stewart, R. M., and Watkin, J. H.: Brain **60**: 149, 1937.
2. Caffey, J.: Pediatric X-ray Diagnosis, Chicago, 1950, Year Book Publishers, pp. 483, 823, 838.
3. Dale, T.: Acta radiol. **12**: 237, 1931.
4. Davis, D. B., and Currier, F. P.: J. A. M. A. **102**: 2173, 1934.
5. Einhorn, N. H., Moore, J. R., Ostrum, J. W., and Rowntree, L. G.: Am. J. Dis. Child. **61**: 776, 1941.
6. Ellis, R. W. B.: Proc. Roy. Soc. Med. **31**: 770, 1938.
7. Ellis, R. W. B., Sheldon, W., and Capon, N. B.: Quart. J. Med. **5**: 119, 1936.
8. Engeset, A., Imerslud, O., and Blystad, W.: Acta radiol. **36**: 1, 1951.
9. Evans, P. R.: Proc. Roy. Soc. Med. **29**: 500, 1936.
10. Evans, P. R.: Proc. Roy. Soc. Med. **30**: 1071, 1937.
11. Fairbank, T.: An Atlas of General Affections of the Skeleton, Edinburgh, 1951, E. & S. Livingstone, p. 340.
12. Harris, H. A., and Russell, A. E.: Proc. Roy. Soc. Med. **26**: 779, 1933.
13. Henderson, J. L.: Arch. Dis. Child. **15**: 200, 1940.
14. Hunter, C.: Proc. Roy. Soc. Med. **10**: 104, 1917.
15. Hurler, G.: Ztschr. f. Kinderheilk. **24**: 220, 1919.
16. Jackson, W. P. U.: Arch. Dis. Child. **26**: 549, 1952.
17. Jewesbury, R. C., and Spence, J. C.: Proc. Roy. Soc. Med. **14**: 27, 1921.
18. Knaggs, R. L.: Brit. J. Surg. **11**: 757, 1924.
19. Knaggs, R. L.: Ibid. **15**: 10, 1927.
20. Knaggs, R. L.: Ibid. **16**: 370, 1929.
21. Kressler, R. J., and Aegerter, E. E.: J. PEDIAT. **12**: 579, 1938.
22. Lindsay, S., Reilly, W. A., Gotham, T. J., and Skahen, R.: Am. J. Dis. Child. **76**: 239, 1948.
23. Morquio, L.: Arch. méd. enf. **32**: 129, 1929.
24. Morquio, L.: Ibid. **38**: 5, 1935.
25. Park, E. A.: The Harvey Lectures **34**: 157, 1938-39.
26. Pohl, J. F.: J. Bone Joint Surg. **21**: 187, 1939.
27. Rogers, W. A.: Experience in the Management of Fracture and Dislocations, P. D. Wilson, ed., London, 1938, J. B. Lippincott Co., p. 403.
28. Ruggles, H. E.: Am. J. Roentgenol. **25**: 91, 1931.
29. Smith, J.: Proc. Roy. Soc. Med. **26**: 1019, 1933.
30. Strauss, L.: Am. J. Path. **24**: 855, 1948.
31. Thomsen, G., and Vesterdal, D.: Acta radiol. **35**: 331, 1951.
32. Wheeldon, T. F.: Am. J. Dis. Child. **19**: 1, 1920.

OSTEOGENESIS IMPERFECTA CONGENITA: A CONNECTIVE TISSUE DIATHESIS

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IT IS an honor and a pleasure to be asked to contribute to this anniversary number in honor of Dr. Park. Furthermore, it is gratifying to be able to make a small contribution to a subject in which Dr. Park excels. He first introduced me to diseases of bone a number of years ago and has continued to stimulate and teach me ever since.

At the present time, when so much attention is being focused on the connective tissues and their diseases, any new observations in this field would seem worthy of recording. We should therefore like to present a typical case of osteogenesis imperfecta congenita and to detail and discuss certain heretofore unreported morphological aspects of this syndrome.

CASE REPORT

Autopsy (22803): The body was that of a Negro infant weighing 1,400 grams. The baby was delivered after a prolonged labor (fourteen hours) and was presumably near term. The child died after twenty-seven minutes. The parents were normal as were three siblings, one of whom was delivered ten months after the birth of the present patient.

External Appearance: There was marked symmetrical shortening of the four extremities, which tended to taper off at the ends in characteristic fashion and give the appearance of micromelia (Fig. 1, *A*). The proportions of the body and head did not appear abnormal. The scleras were dark in color. The eyes did not appear enlarged. The skin seemed unusually thin.

Abdominal Cavity: The contents of the abdominal cavity appeared normal. The liver weighed 115 grams (normal for 3,000 grams is 135 grams). The spleen weighed 10 grams (normal for 3,000 grams is 10 grams).

Thoracic Cavity: The contents of the thoracic cavity were entirely normal.

Cranial Cavity: On cutting through the calvarium there appeared to be no bone whatsoever. There was extensive subdural and subarachnoid hemorrhage.

Extremities: On cross section the epiphyseal cartilages appeared normal in size for a full-term infant. There was a well-developed center of ossification in the upper end of each tibia. There was great shortening of the diaphyses with numerous fractures of all extremities as well as the ribs. The costochondral and epiphyseal-diaphyseal junctions were straight. In the fracture areas there was thickening of the cortex. Elsewhere it was thin and in places appeared not to be present at all.

Microscopic Findings.—Tissues from all organs were fixed in Zenker-formol and formalin alone, embedded in paraffin, cut, and stained with hematoxylin and eosin. Certain tissues were stained with 2 per cent silver nitrate, the Gomori[1] ammoniacal silver procedure, the McManus[2]-Lillie[12]-Hotchkiss[3] periodic acid-Schiff reaction, and toluidine blue.

Skin: In hematoxylin-eosin preparations the epidermis appeared normal when compared with that of children of weights ranging from 1,300

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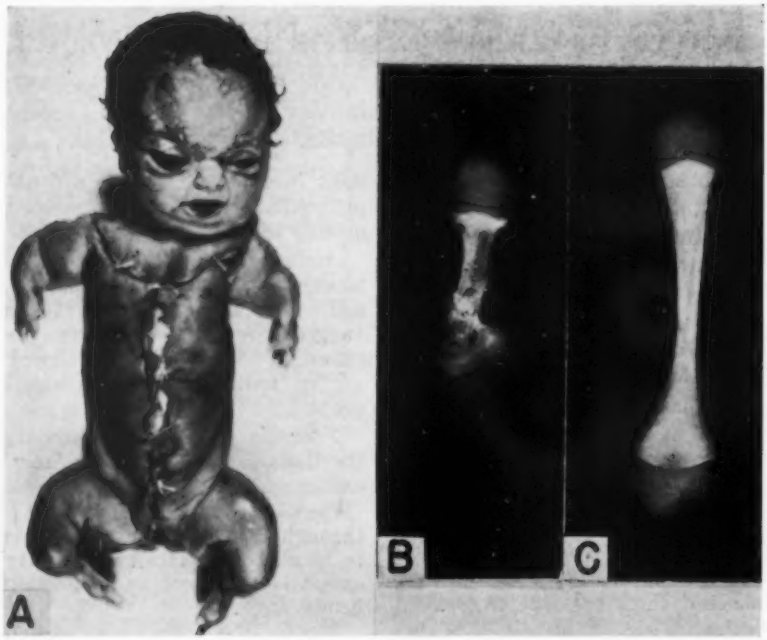

Fig. 1.—*A*, External appearance of infant, showing marked deformity of the extremities. *B* and *C*, Roentgenograms of humerus of case being described (*B*) and normal (*C*). Note difference in length and similarity in size of epiphyseal cartilages. Fractures and bony proliferation in diaphysis are striking.

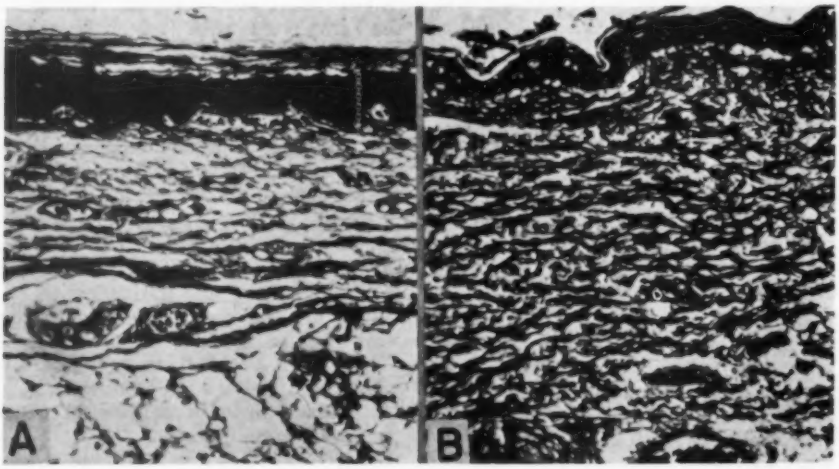

Fig. 2.—*A*, Gomori silver stain[1] of skin of patient in comparison with normal skin of infant weighing 1,500 grams (*B*). Note thin argyrophilic fibers making up the narrow corium (*A*) in comparison with thicker dermis (*B*) made up of stouter nonargyrophilic fibers.

to 3,000 grams. The fibers of the corium, however, were much thinner in the case being described. When stained specially the thin fibers were argyrophilic (Fig. 2), conforming with this criterion for reticulum, were metachromatic, and exhibited a red color with the periodic acid-Schiff reagents. The fibers of mature corium, of course, were not argyrophilic or metachromatic.

Eye: The corneas of both eyes were thinner than normal. There was no abnormality of the epithelial layer. The underlying substantia propria was composed of thin fibers, much more delicate than normal (Fig. 3, *A* and *B*). In addition these fibers were argyrophilic and metachromatic and stained red with the periodic acid-Schiff procedure.

The sclerotic coat of the eyes from the infant with osteogenesis imperfecta was thinner than that from normal individuals of the same weight or weighing 3,000 grams. The fibers were more delicate (Fig. 3, *C* and *D*) and gave a positive silver staining reaction and were metachromatic. In addition they were positive to the periodic acid-Schiff stain, exhibiting a red color.

Skeletal Tissues: Sections of costochondral junctions, a number of the epiphyseal-diaphyseal junctions of the long bones and the skin, subcutaneous tissues of the scalp, and the dura of the head were examined.

As noted grossly, in the epiphyseal cartilage of the upper humerus a center of ossification was found. Here the cartilage cells appeared to be growing in normal fashion and spicules of cartilage matrix, impregnated with inorganic materials, were being produced as a result of disappearance

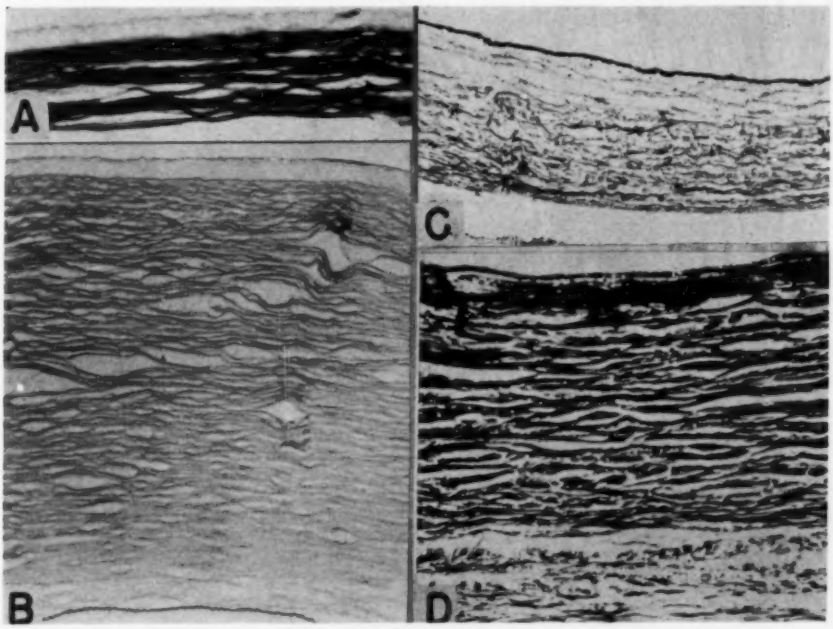

Fig. 3.—*A* and *B*, Corneas from infant being described and control stained with periodic acid-Schiff technique. In addition to marked difference in width the former stains red while the latter is almost colorless. *C* and *D*, Scleras from infant with osteogenesis imperfecta and normal infant. These exemplify difference in thickness and thin reticulum found in former (silver stain).

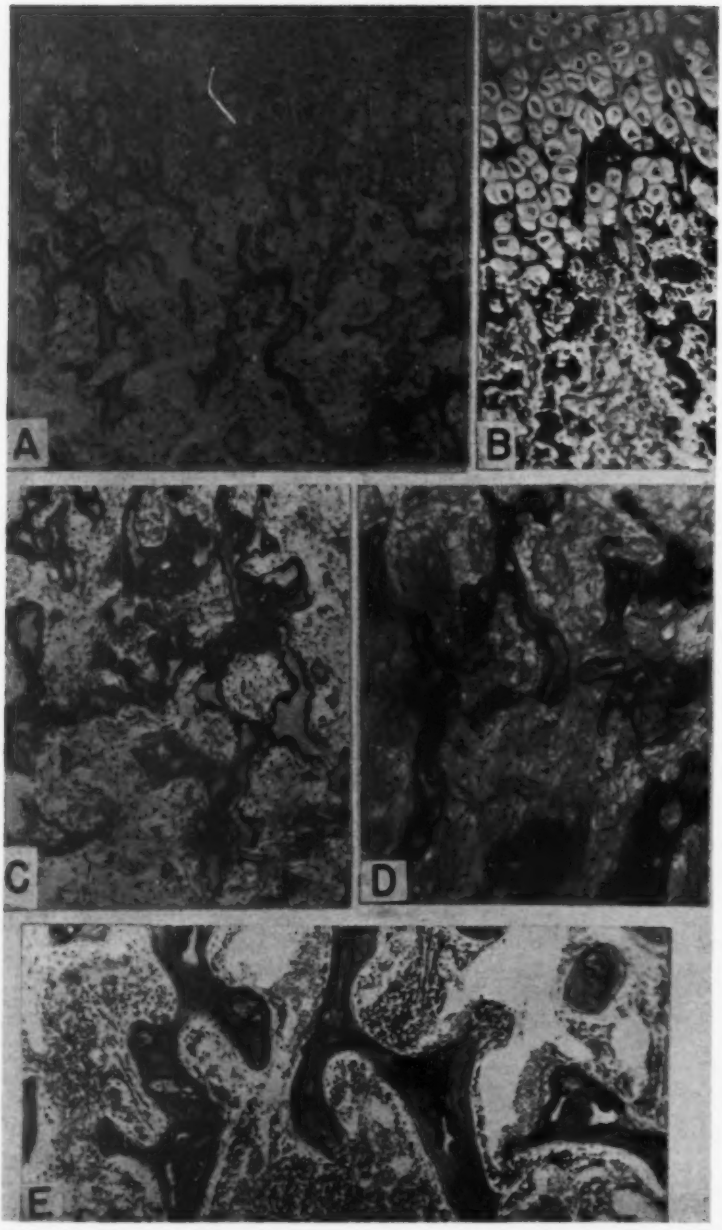

Fig. 4.—*A*, Cartilage shaft junction of upper tibia to show maturation of cartilage cells and bone matrix beneath. Silver nitrate treatment of undecalcified section, *B*, shows normal deposition of inorganic materials in matrix. *C*, Hematoxylin and eosin-stained section of metaphyseal region of upper tibia to show rim of deep blue material about spicules of cartilage matrix. *D*, Periodic acid-Schiff stain to show intense staining of material noted above. *E*, Area in diaphysis where healing of fracture has occurred. Three zones from within-out are seen: original cartilage matrix, peculiar basophilic and periodic acid-Schiff positive material, and normally appearing bone.

of the hypertrophic cartilage cells. However, at this point any similarity to normal growth sequences ceased. Osteoblasts were not to be found and no osteoid (or bone) was therefore present on the framework of calcified cartilage matrix. A similar situation existed at the cartilage shaft junctions (Fig. 4, *A*); that is, the growth deposition of inorganic salts was demonstrated conclusively by staining undecalcified sections with 2 per cent silver nitrate (Fig. 4, *B*). Another abnormality not so prominent in the slower growing center is also clearly made out; at the cartilage-shaft junction the spicules of calcified cartilage matrix did not appear to be under-

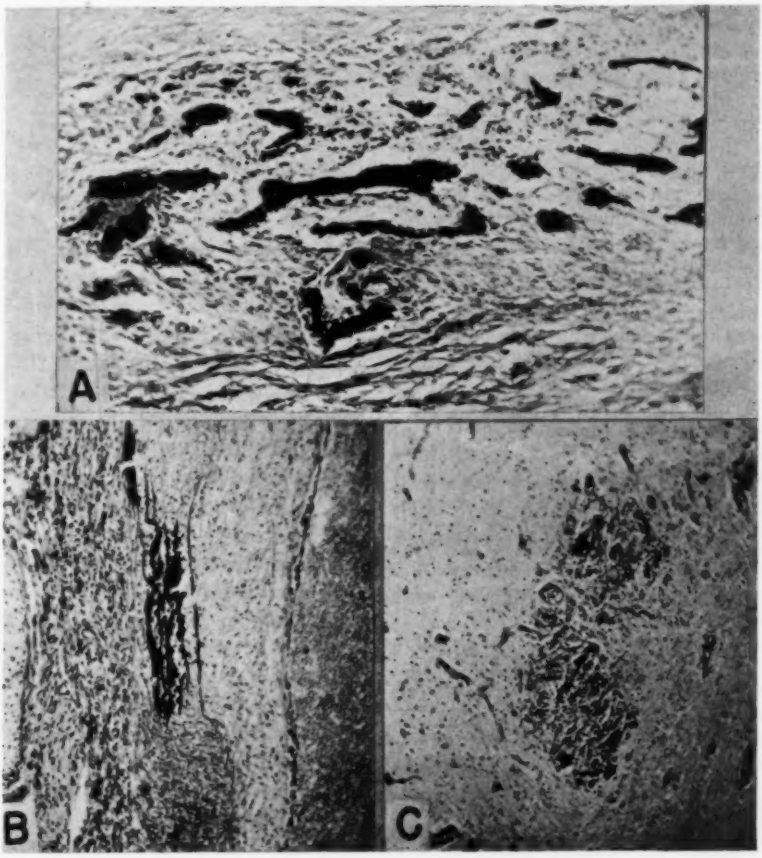

Fig. 5.—*A*, Microscopic foci of membranous bone formation in scalp. *B*, Section of wall of pulmonary artery to show thickening and calcification. *C*, Focus of calcification and glial proliferation in brain.

of cartilage, its invasion by blood vessels, and the deposition of inorganic materials in the matrix between the hypertrophic cells which are being invaded were entirely normal. The going destruction. More prominent was the absence of osteoblasts; consequently there was a lack of osteoid or bone on the framework of calcified cartilage matrix. Therefore, just as

in scurvy, numerous fractures of this framework were found. In such areas there were sometimes red blood cells but even more prominent was a pink-staining eosinophilic material such as one encounters in scurvy[5] or in rarefying diseases of bone such as leukemia.[6]

Further down in the lower part of the metaphysis there was another abnormality. In partially decalcified hematoxylin-eosin preparations light blue-staining spicules of calcified cartilaginous matrix were coated with a deep blue-staining layer of a substance which stains also intensely red with the periodic acid-Schiff reagents (Fig. 4, *C* and *D*). The red color was more intense than one ever encounters in bone or cartilage. It was not affected by saliva; hence it was not free polysaccharide. Its nature could not be further characterized by histochemical procedures save to say that it was metachromatic. In undecalcified sections it was not darkened by silver nitrate.

Further down in the shaft where fractures of the calcified matrix and cortex of the diaphysis occurred there was bone formation, both periosteal and endosteal, going on in normal fashion. Hence, trabeculae consisting of three layers, calcified cartilage matrix, the zone of blue-staining material described above, and bone, were found (Fig. 4, *E*).

In sections of skin and dura, which were thought to contain no bone grossly, small islands of membranous bone were present (Fig. 5, *A*). The insufficient osseous tissue which was present appeared normal. The degree of development was comparable to that which might be expected in an embryo of 2 to 3 months of age.

Lungs: In several large pulmonary arteries there was marked proliferation of the endothelium (Fig. 5, *B*) and foci of calcification in the underlying media. The remainder of the tissues was normal.

Brain: Scattered through the brain there were numerous small vessels with deep blue-staining refractile walls. In addition similar material was found as extravascular granules in the parenchyma (Fig. 5, *C*). In such foci the glial cells had proliferated. This material gave positive silver and iron reactions.

Other Tissues: Particular attention was directed to the connective tissue of all other organs. No abnormality was demonstrated.

DISCUSSION

Osteogenesis imperfecta congenita would appear to be fairly easy to diagnose from the gross appearance: deformities of the extremities, thin skin, and dark sclera. The only possible skeletal abnormality which might be a cause for confusion is achondroplasia. However, when compared grossly, microscopically, and roentgenographically, these two disorders are entirely different.

Before commenting on the significance of the findings in the autopsy described above it is necessary to say something concerning current concepts of the nature of reticulum and collagen. The former term was applied by Mall[7] to the extremely fine fiber networks found in such organs as the spleen and lungs. Some years later as a result of Maresch's modification of Bielschowsky's silver impregnation method it was found[8] that these fine fibers were argyrophilic while the stouter, broader ones were not. As a result argyrophilia became a criterion for reticulum, and argyrophobia a characteristic of collagen. There has been pretty general agreement that reticulum is a precursor of collagen. This concept has been based on studies of the corium in healing skin wounds, in infectious granulomas, and particularly in the organization of blood

clots in scorbutic guinea pigs treated with vitamin C.[9] More recently further evidence has been brought forth by the use of the electron microscope and x-ray diffraction techniques. Employing the former in studying the transition of argyrophilic reticulum in newborn rat skin to argyrophobic collagen in the adult animal, Gross[10] has found that both exhibit the same characteristic average periodicity of 640 Å and that only the fiber width varies, i.e., newborn animal, 500 to 600 Å versus 60-day-old rat, 13,000 to 15,000 Å. Both types of fibers have the same x-ray diffraction pattern.[11] The basis for the difference in silver staining has not been clearly defined. Gross[11] has determined that electron photomicrographs of silver-stained reticulum fibers show irregular surface adsorbtion of metal particles of colloidal dimensions in random fashion. Purplish staining collagen fibers, on the other hand, appear to adsorb particles varying in size and shape. Gross[11] points out that skin containing reticulum is more gelatinous than adult collagenous skin. Could such gelatinous material be implicated in argyrophilia? Such a possibility must not be overlooked since reticulum in the embryo is metachromatic and newly formed argyrophilic fibers in healing scurvy also stain red with toluidine blue.[5] Metachromasia is a characteristic of tissues containing mucopolysaccharides though the specific chemical reactions are not understood.

Another stain of interest, the periodic acid-Schiff reaction first introduced by McManus,[2] was shown by Lillie[12] to demonstrate reticulum.

The presence of thin skin in individuals with osteogenesis imperfecta has been commented upon in previous descriptions of autopsied cases.[14, 15, 16] However, no studies employing more specialized stains have been reported. It is therefore of great interest to find that in this supposedly full-term infant argyrophilic, metachromatic, and periodic acid-Schiff positive reticulum fibers make up the corium rather than argyrophobic, nonmetachromatic, and periodic acid-Schiff negative fibers. It would appear that the corium is greatly retarded in development and resembles that seen in the early embryo.[4]

It must be pointed out at this time that although this infant weighed only 1,400 grams and should therefore be classed as a premature infant (e.g., under 2,500 grams) according to the menstrual history, it was full term and furthermore a center of ossification was present in the upper epiphyseal cartilage of the tibia, something virtually never seen in a premature infant. From the great decrease in skeletal mass and size of the extremities one might expect a marked effect on body weight. A similar situation has been noted in a case reported by Weber.[17]

The thin scleras and corneas noted above are, at least, in the case of the former, not unexpected. "A bluish tinge of the eyeball" as a part of the osteogenesis imperfecta syndrome was noted by Spurway in 1896[18] and four years later Eddowes[19] related the blue color to a lack of fibrous tissue. However, no special stains have been applied to the sclera so that it is of interest to find that the thin scleras are composed of argyrophilic, meta-

chromatic, and periodic acid-Schiff positive reticulum, rather than thicker, mature collagen fibers. The thin corneas which also stain intensely with the periodic acid-Schiff procedure further indicate a disturbance in connective tissue maturation. The ocular tissue disturbances in this and other cases will be detailed elsewhere by Dr. Albert D. Ruedemann, Jr.[20]

So-called membranous bone formation which takes place normally in certain bones of the calvarium and a portion of the clavicle is quite similar to matrix production by the osteoblast and periosteal cells. The basic morphological change is the appearance of organic matrix consisting of fibers and interfibrillar material in the vicinity of specialized mesenchymal cells (osteoblasts). It is quite likely that such cells promote the appearance of this matrix but how they mediate the synthesis its two prominent constituents, the protein, collagen, and the polysaccharide moiety, consisting of hexose amine and hexuronic acid, are questions that have yet to be answered.

Failure to produce bone matrix is the fault in osteogenesis imperfecta. This, of course, has been commented upon in a number of reports.[15, 17, 21, 22, 23, 24] So, too, the absence of any abnormality in the growth and maturation of epiphyseal cartilage and in the deposition of inorganic materials in cartilage matrix has been well recognized. The similarity of the morphological changes in osteogenesis imperfecta and scurvy, for one cannot look at sections of bone from the former without thinking of the latter, has also been commented upon elsewhere.

One of the most interesting, yet difficult, phenomena to explain is the prompt stimulation of osteoblastic activity when fractures occur. What the stimulus may be is, of course, an extremely important matter to determine. Likewise the activity of fibroblasts in the corium does not appear to be impaired in this syndrome since wounds heal in normal fashion in children and adults.[13]

The eosinophilic material about the fractures of calcified cartilaginous matrix is quite similar to that which is encountered in scurvy. This pink-staining substance has not as yet been characterized histochemically.[5]

The blue-staining material which colors so red with the periodic acid-Schiff reaction is unique in our experience with bone disease. Cartilage matrix and osteoid may stain pale pink but never as red as this peculiar material, which we have noted above is not impregnated with inorganic substances. The studies of Heller-Steinberg[25] have not revealed such intense red-staining matrix even in thick sections (20 micra).

It is to be regretted that the teeth in this infant were not saved for microscopic examination.

It would appear that osteogenesis imperfecta is a systemic disturbance of connective tissue in certain areas. This is not a new concept, since, based on the failure of bone matrix to develop, it is one which has been advanced by others.[16, 17, 23, 24] However, the histochemical studies described above which demonstrate a disturbance in the differentiation of reticulum into adult collagen fibers, place this concept on a much firmer foundation.

SUMMARY

A case of osteogenesis imperfecta in a newborn infant has been reported. The failure of reticulum to differentiate into mature collagen has been demonstrated in the corium, sclera, and cornea. The presence of a material in the bones which stains intensely with the periodic acid-Schiff technique and which may be an immature form of bone matrix has been described.

REFERENCES

1. Gomori, G.: Silver Impregnation of Reticulum in Paraffin Sections, Am. J. Path. **13**: 993, 1937.
2. McManus, J. F. A.: The Histological Demonstration of Mucin After Periodic Acid, Nature **158**: 202, 1946.
3. Hotchkiss, R. D.: A Microchemical Reaction Resulting in the Staining of Polysaccharide Structures in Fixed Tissue Preparations, Arch. Biochem. **16**: 131, 1948.
4. Follis, R. H., Jr.: Personal observations.
5. Follis, R. H., Jr.: Histochemical Studies on Cartilage and Bone. II. Ascorbic Acid Deficiency, Bull. Johns Hopkins Hosp. **89**: 9, 1951.
6. Follis, R. H., Jr., and Park, E. A.: Some Observations on the Morphologic Basis for the Roentgenographic Changes in Childhood Leukemia, Bull. Hosp. Joint Dis. **12**: 67, 1951.
7. Mall, F. P.: Reticulated Tissue and Its Relation to the Connective Tissue Fibrils, Johns Hopkins Hosp. Rep. **1**: 171, 1896.
8. Schmidt, E.: Ueber die Stutzsubstanz der Leber im normalen und pathologischen Zustand, Beitr. z. path. Anat. u. z. allg. Path. **42**: 606, 1907.
9. Wolbach, S. B.: Controlled Formation of Collagen and Reticulum. A Study of the Source of Intercellular Substance in Recovery From Experimental Scorbutus, Am. J. Path. **9**: 689, 1933.
10. Gross, J.: Aging of Collagenous Connective Tissue of Rat Skin as Studied with the Electron Microscope, Am. J. Path. **26**: 708, 1950.
11. Gross, J.: Connective Tissue Fine Structure and Some Methods for Its Analysis, J. Gerontol. **5**: 343, 1950.
12. Lillie, R. D.: Reticulum Staining With Schiff Reagent After Oxidation by Acidified Sodium Periodate, J. Lab. & Clin. Med. **32**: 910, 1947.
13. Johnson, R. W.: Personal communication.
14. Blegvd, O., and Haxthausen, H.: Blue Sclerotics and Brittle Bones With Macular Atrophy of the Skin and Zonular Cataract, Brit. M. J. **2**: 1071, 1921.
15. Siedorf, K. S.: Osteogenesis Imperfecta, 1949, Universitetsforlaget, Arhus, Denmark.
16. Gruber, G. B.: Zur Kenntnis und Kritik der Osteogenesis imperfecta congenitalis, Arch. path. Anat. **316**: 317, 1949.
17. Weber, M.: Osteogenesis Imperfecta Congenita. A Study of Its Histopathogenesis, Arch. Path. **9**: 984, 1930.
18. Spurway, J.: Hereditary Tendency to Fracture, Brit. M. J. **2**: 844, 1896.
19. Eddowes, A.: Dark Sclerotics and Fragilitas Ossium, Brit. M. J. **2**: 222, 1900.
20. Ruedemann, A. D.: To be published.
21. Harbitz, F.: Ueber Osteogenesis imperfecta, Beitr. z. path. Anat. u. z. allg. Path. **30**: 605, 1901.
22. Kardamatis, C.: Anatomische Befunde der Osteogenesis imperfecta, Arch. path. Anat. **212**: 436, 1913.
23. Bauer, K. H.: Ueber Osteogenesis imperfecta. Zugleich ein Beitrag zur Frage einer allgemeinen Erkrankung samtlicher Stutzgewebe, Deutsche Ztschr. f. Chir. **154**: 166, 1920.
24. Jeckln, E.: System gebundene mesenchymal Erschopfung. Eine neue Begriffsfassung der Osteogenesis imperfecta, Arch. path. Anat. **280**: 351, 1931.
25. Heller-Steinberg, M.: Ground Substance, Bone Salts, and Cellular Activity in Bone Formation and Destruction, Am. J. Anat. **89**: 347, 1951.

VASCULAR COMPLICATIONS OF JUVENILE DIABETES

Analysis of Forty Patients After Ten Years of Disease

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IN THE fall of 1930, as the special clinics were coming to life in the Harriet Lane Home under the direction of Dr. Park, the diabetic clinic was born. Three small boys comprised the charter membership. Two of these, aged 3 years, had just started their diabetic careers a few months previously; the third, aged 6 years, had already had his disease for two and a half years. A brief summary of the life history of these three boys, all of whom are included in the survey to be reported, illustrates the widely divergent courses that may be pursued and the possible results to be expected.

Since the start of the clinic in 1930, approximately 250 patients have been treated and followed for variable periods of time. Although the upper age limit in the pediatric clinic is 13 years, these patients, starting in childhood, have been kept under observation through the no man's land of adolescence. In most instances, medical supervision has been very close during the early years of the disease and attendance at clinic quite regular. During the later years, as the patients have asserted their independence in adolescent fashion, regulation has tended to be less well supervised and attendance at clinic more sporadic, with absences sometimes as long as two or three years. Lack of social service help, which was a valuable feature of the clinic during the first half of its existence, but which has become practically unavailable since the war, has been partly responsible for this and also for an increasing irregularity in attendance of the younger group as well, after their first few years.

Management of the diabetes itself over this period of twenty-two years has been modified from time to time with the growing awareness of the total problem of diabetes in the child, although there has been very little change in the type of diet since about 1935, when the need for a normally proportioned diet, with more generous carbohydrate content than had previously been provided, was recognized. At first perfectionistic, with insistence on careful measurement of all portions of the diet at all times and with an effort to keep the urine sugar-free, the approach has gradually become more liberal with modification of dietary restrictions as the patient has become adjusted to his disease, and with acceptance of a measure of glycosuria as not only compatible with satisfactory regulation, but also conducive to greater stability through more successful avoidance of insulin reactions. Some of the more uncooperative patients who have disregarded all instructions and the careless ones who

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have followed the path of least resistance have settled into a way of life that unintentionally provides a control group for comparison with those whose disease has been more carefully regulated.

In most of the patients, regular or crystalline insulin has been used for initial regulation and has been continued for the first two or three years of the disease, while patient and mother are being taught the elements of diabetes and while two doses a day suffice for satisfactory regulation. The period of treatment with regular insulin was necessarily longer in those in whom the onset of diabetes antedated the arrival of protamine insulin. Likewise, in a few patients who developed diabetes at the start of the protamine era, treatment with protamine insulin alone was instituted at the very beginning. When, however, it was found that regular insulin eventually had to be given in addition to the protamine, and that the inflexibility in the action of protamine insulin in meeting emergencies sometimes caused difficulty during the elementary period of instruction referred to above, it became routine to start all patients on regular or crystalline insulin, shifting to protamine with regular when two doses daily no longer provided satisfactory control or when fasting levels of blood sugar exceeded reasonable limits. It will be observed, on reference to the tables, that two of the patients who have passed the ten-year mark are still on crystalline insulin alone. One of these, who had been on protamine insulin for a while, returned to the regular insulin of his own accord, without seeking medical advice, after experiencing a severe reaction to protamine; the other, a seriously retarded child with epilepsy, has been kept on regular insulin because his convulsions occur during the early morning hours when they might be confused with hypoglycemic convulsions, if he were on the protamine regime. It will also be noted that four of the older patients are now receiving NPH insulin.

On the present routine, each patient, at the beginning of his diabetic career, is placed on a measured diet, using scales for accuracy. This is followed in detail, while instruction in the nature of the disease and in the elements of the diet is in progress, and familiarity with the use of insulin is acquired. As child and mother become well versed in these details and gain confidence, greater freedom in substitutions is introduced. Instruction is then given with regard to the particular foods, of low carbohydrate or low available carbohydrate content, that can be taken in any amount desired without reference to measurements initially prescribed. After several years of this regime, with the continued use of scales for the foods of high carbohydrate content, that should be measured, the scales are finally discarded, as the patient, now thoroughly educated in the management of his disease, has acquired good dietary habits and the art of self-control. From here on the patient who has cooperated in this educational regime more or less automatically pursues a satisfactory course, choosing a suitable diet, reasonably uniform in carbohydrate content and distribution from day to day, without thought of weights and measures. When such a patient, under special circumstances, departs radically from his routine he does so, knowing what he is doing and how to

TABLE I. ANALYSIS OF THE FORTY PATIENTS WITH

PATIENT	AGE AT ONSET	YEARS OF DISEASE	CONTROL (5-YEAR PERIODS)			GENERAL PHYSICAL FINDINGS				OPHTHALMOSCOPIC		URINE		BLOOD (MG. %)		PHTHALEIN EXCRETION (%)				
			FIRST	SECOND	THIRD	B. P.	REFLEXES	O. T. (0.1 MG.)	OTHER	DIABETIC RETINITIS	OTHER	ALB.	SED.	NPN	CHOL.	15 M.	30 M.	1 HR.	2 HR.	TOTAL
1. D. B. A 19481	11	11	Fair	Fair	Fair	110/60	Not obtained	Pos.	Dental caries	0	0	0	0	34	270	32	16	10	3	61
2. K. B. 91074	5	17	Good +	Good +	Good	110/70	Active	Neg.	0	0	Refractive error	0	0	31	210	40	20	10	5	75
3. D. C. 92982	4½	11	Good	Good	Good	95/60	Active	Doubtful	0	0	0	0	0	30	290	43	12	12	6	73
4. H. C. 56762	3	22	Fair	Poor	Poor	110/75	Active	Doubtful	Enlarged liver	+	0	0	0	36	200	32	20	18	10	80
5. W. C. A 28857	5	10	Fair	Fair	—	130/80	Active	Neg.	Mental retardation	0	Pallor of discs	0	0	40	344	10	16	15	9	50
6. C. D. 63235	3	20	Fair	Fair	Fair	124/80	Sluggish	Neg.	Dental caries	?	Refractive error	+	0	41	270	32	20	10	5	67
Second survey		22	Fair	Fair	Fair	125/80	Sluggish	Neg.	Dental caries	++ +	Refractive error	0	0	42	266	15	15	15	20	65
7. D. D. A 896	3½	13	Good	*	*	104/50	Active	Pos.	0	0	0	+	0	29	180	40	20	15	5	80
8. A. E. A 4372	12	16	Good	Fair	Poor	130/90	Active	Neg.	Poor oral hygiene	Right ++ Left–Hemorrhage & exudate–Not typical		0	0	38	224	0	25	20	10	55
9. C. E. 62864	7	18	Fair	Fair	Fair	138/80	Not obtained	Neg.	Dentures	++ ++	0	+	Occ. RBC	36	434	35	20	9	7	71
10. B. F. A 30570	12	10	Fair	Poor	—	120/70	Active	Neg.	Pyorrhea	0	0	Trace	0	28	380	44	22	11	—	77
11. B. G. A 22937	4	11	Good	Fair +	Good —	120/80	Active	Neg.	Abscess buttock	0	0	0	0	40	234	—	50	25	5	80
12. D. G. A 19918	3	10	Good +	Good +	—	110/60	Active	Pos.	0	0	0	0	0	32	300	15	30	20	4	69
13. S. G. A 18394	12	10	Fair	Fair —	—	140/85	Active	Neg.	Mental retardation	+	0	0	0	29	350	50	15	15	5	85
Second survey		12	Fair	Fair —	Fair	130/90	Active	Neg.	Exophthalmos	+	0	Trace	0	30	420	25	10	10	5	50
14. B. H. A 26715	12	10	Good —	Fair	—	110/80	Active	Neg.	0	0	Congenital opacities	0	0	40	380	15	25	25	10	75
15. G. K. 69772	12	10	Poor	Fair to Good	—	126/80	Active	Neg.	Dental caries	+	0	0	0	42	334	27	15	23	8	73
16. I. K. A 5446	9	13	Good +	Good	Good —	125/80	Sluggish	Neg.	Linear scleroderma	0	0	0	0	29	276	40	30	20	5	95
17. J. K. 74609	2	21	Fair	?	Fair	120/70	Active	Neg.	Pyorrhea	++	Vitreous hemorrhage left eye	0	0	35	250	—	55	10	5	70
18. S. K. A 36414	9	10	Good —	Fair	—	120/60	Active	Neg.	Very tall	0	0	0	0	34	250	16	40	22	10	88
19. T. K. A 29207	4	11	Fair	Fair	Fair	115/70	Active	Neg.	0	0	0	0	0	30	304	28	30	20	7	85
20. V. K. A 7499	4	14	Good —	Fair	Fair —	130/80	Sluggish	Pos.	0	+	0	0	0	29	234	15	35	45	5	100

*Patient 7 (D. D.) was treated with insulin during the first four years of diabetes, with dosages as high as 30 units daily. At the end of the fourth year his insulin requirement steadily declined until it was discontinued altogether. He has since done well for nine years without requiring insulin again. The diagnosis of diabetes was established at onset by glucose tolerance tests and was supported by a strong family history of diabetes. An orthostatic albuminuria accounts for the albumin reported on urinalysis. This patient is to be the subject of a later report.

DIABETES OF MORE THAN TEN YEARS' DURATION

X-RAY STUDIES		SKIN RESISTANCE (INCREASE)	MISCELLANEOUS DATA	DATE OF BIRTH	YEAR OF SURVEY	SEX	RACE	F. H. DIABETES	ILLNESS (NON-DIAB.)	PUBERTY COMPLETE	OCCUPATION	MARRIAGE AND CHILDREN	DIET AT LAST CALCULATION			PRESENT INSULIN DOSAGE
CHEST	LEGS FOR ARTERIAL CALCIFICATION												P	F	CH	
Normal	None	.....		8/26/28	1950	M	W	1	0	15	Steel worker	Married 1952	100	130	210	C 22 P 20
Normal	None (Phleboliths)	.....		8/24/29	1951	F	W	0	0	13	College	.....	100	90	215	C 12 P 64
Normal	None	.....		8/19/34	1950	F	W	0	Rheumatic fever	13	School	.....	90	70	200	C 25 P 27
Chronic bronchitis	Posterior tibials	.....		6/20/24	1950	M	W	0	Chronic bronchitis	20(+) Delayed	Clerk	.....	?	?	?	C 25-5-15-5
Normal	Doubtful	Marked on feet		12/30/37	1952	M	W	0	Epilepsy	15	(Retarded)	.....	100	110	250	C 40-30-20
Normal	Posterior tibials	.....		6/27/27	1950	M	W	1	0	16(−)	Shipyard	Married 1 child	100	100	250	C 30 P 50
Normal	Posterior tibials	.....			1952	.....		1	0	.....	Wire mill	Married 2 children	100	100	250	C 30 P 50
Normal	None	.....		10/17/33	1950	M	W	3	0	16	School	.....	*	*	*	*
Normal	None (Phleboliths)	.....		10/15/24	1952	M	W	3	Numerous accidents	?	Farmer	Married 2 children	150	100	300	C 15 P 25
Normal	Dorsalis pedis	.....		3/29/26	1951	M	W	0	0	17(−)	Dock worker	.....	110	135	225	C 25 P 60
Normal	None (Phleboliths)	.....		1/ 6/31	1952	F	W	0	Toxemia of pregnancy	15	.....	Married Therapeutic abortion	70	65	150	C 35 P 25
Normal	None	.....		5/22/37	1952	F	W	0	?Rheumatic fever	14(+)	School	.....	80	65	180	C 40 P 70
Normal	None	Normal		1/14/38	1951	M	W	1	0	.....	School	.....	110	90	230	C 18 P 28
Normal	None	.....		12/11/27	1950	F	W	1	0	12	.....	Married (twice) No children	95	110	175	C 11 P 36
Normal	None	.....		.....	1952	.....		1	Hyperthyroidism	.....	.....	Married (twice) No children	95	55	195	NPH 45
Normal	None	.....		5/ 5/30	1952	F	W	2	0	14	Beautician	.....	85	50	180	C 40 P 58
Normal	Anterior and posterior tibials	Marked on feet		11/19/30	1952	F	C	1	0	12	Housework	Married;1 therapeutic abortion,2 stillbirths	100	80	200	C 15 P 45
Normal	None	.....		5/ 7/30	1952	F	W	2	Linear scleroderma left face	13	College	.....	75	50	160	C 24 P 28
Normal	None	Small spots on feet		5/23/29	1952	F	W	0	0	13	Factory Worker	Married	95	75	180	C 35 P 38
Normal	None	.....		3/24/31	1952	M	W	0	0	14	Radio installer	.....	125	95	235	C 50 P 80
Normal	None	.....		7/30/34	1950	M	W	3	0	15	School	.....	130	130	245	C 20 P 42
Normal	None	.....		11/ 9/33	1952	M	W	0	0	17	Clerk grocery store	.....	100	105	250	C 24 P 45

	PATIENT	AGE AT ONSET	YEARS OF DISEASE	CONTROL (5-YEAR PERIODS)			GENERAL PHYSICAL FINDINGS				OPHTHALMOSCOPIC		URINE		BLOOD (MG. %)		PHTHALEIN EXCRETION (%)				
				FIRST	SECOND	THIRD	B. P.	REFLEXES	O. T. (0.1 MG.)	OTHER	DIABETIC RETINITIS	OTHER	ALB.	SED.	NPN	CHOL.	15 M.	30 M.	1 HR.	2 HR.	TOTAL
21.	J. L. 86769	1	18	Good +	Good	Good	104/50	Sluggish	Pos.	0	0	0	0	0	32	234	45	15	10	—	70
22.	A. M. A 14577	5	11	Good	Fair	Fair	110/60	Active	Neg.	0	0	0	0	0	35	230	40	20	15	5	80
23.	J. M. 65160	2	22	Good +	Good +	Good +	120/60	Sluggish	Pos.	Bursitis rt. knee	0	0	0	0	39	300	45	20	5	0	70
24.	J. M. A 446	3	17	Good	Good	Good	120/80	Active	Pos.	0	++	Exudate and flame-shaped hemorrhages	+	0	25	284	35	25	15	7	82
	Second survey		19	Good	Good	Good	112/72	Active	—	0	++	0	+	0	39	244	30	20	5	5	60
25.	W. M. 90392	8	15	Fair	Fair	Fair	110/60	Sluggish	Pos.	0	—	—	0	0	30	188	40	20	18	10	88
	Second survey		17	Fair	Fair	Fair	100/60	Sluggish	—	0	0	Slight opacities both lenses	0	0	31	224	40	10	10	5	65
26.	A. N. 96198	1	14	Good +	Good +	Good	120/70	Active	Neg.	0	0	0	0	0	37	356	45	25	10	5	85
27.	J. N. 30348	6	12	Fair	Good	Good	120/70	Active	Neg.	0	0	0	0	0	27	214	35	30	15	10	90
28.	E. R. A 3348	12	13	Fair	Fair +	Good —	130/88	Active	Pos.	0	0	Lens opacities	0	0	25	290	50	15	12	5	82
29.	E. R. A 17043	13¼	11	Fair +	Fair +	Fair +	110/75	Active	Neg.	Speech defect	0	Congenital opacities	0	0	30	390	60	22	10	5	97
30.	K. R. A 20413	7	11	Fair	Poor	Poor	130/100	Active	Pos.	0	+	0	Trace	0	37	276	45	20	10	5	80
31.	M. R. A 8973	8	13	Poor	Fair?	Poor	115/80	Sluggish	Neg.	0	++	0	Trace to +	0	35	298	—	40	28	12	80
32.	R. S. A 54516	11	13	Fair +	Good +	Good +	112/80	Active	Pos.	0	++	Refractive error	0	0	28	244	45	10	15	5	75
	Second survey		14	Fair +	Good +	Good +	108/64	Active	—	0	—	Refractive error	0	0	38	214	25	35	15	5	80
33.	R. S. A 16708	7	11	Good +	Fair +	Fair +	120/60	Active	Neg.	0	0	0	0	0	36	224	40	20	20	5	85
34.	R. S. A 8241	2	14	Good +	Good	Good —	116/50	Active	Neg.	0	0	0	0	0	31	244	40	30	15	5	90
35.	J. W. 87229	10	16	Poor	Poor	Fair +	130/85	Very sluggish	Neg.	Peripheral neuritis	++ ++	0	Trace to +	0	25	244	30	24	15	6	75
36.	L. W. 24023	13	10	Fair	Fair	—	110/70	Active	Neg.	Pregnant	+	0	Trace	Rare RBC	23	276	35	20	20	5	80
37.	R. W. A 4298	5	10	Fair —	Poor	—	120/80	Active	Neg.	0	0	0	0	0	32	276	12	20	15	5	52
38.	R. W. A 30352	5	10	Good —	Fair	—	110/60	Sluggish	Neg.	0	+	0	0	0	37	224	45	20	15	5	85
39.	T. W. 90914	6	17	Fair	Fair	Poor +	120/75	Active	Pos.	Peripheral neuritis	++	0	0	0	38	344	10	47	10	5	72
	Second survey		18	Fair	Fair	Poor +	120/80	Rt. Active Lt. sluggish	—	0	+	0	0	0	35	234	45	13	5	(lost)	63
40.	R. Z. 69973	8	20	Good	Good	Good	120/70	Active	Pos.	Collapse of left lung	+ Minimal	0	0	0	28	304	30	16	6	7	59

CONT'D

X-RAY STUDIES		SKIN RESISTANCE (INCREASE)		DATE OF BIRTH	YEAR OF SURVEY	SEX	RACE	F. H. DIABETES	ILLNESS (NON-DIAB.)	PUBERTY COMPLETE	OCCUPATION	MARRIAGE AND CHILDREN	DIET AT LAST CALCULATION			PRESENT INSULIN DOSAGE
CHEST	LEGS FOR ARTERIAL CALCIFICATION												P	F	CH	
Normal	None	.....		2/25/33	1952	F	W	0	0	16	Secretary	Just married	75	105	210	C 23 P 58
Normal	None	Small spots on feet		4/ 7/34	1950	M	W	0	0	15	School	.....	120	125	280	C 22 P 54
Healed primary lesion (calc.) rt. upper lobe	Posterior tibials	.....		3/20/27	1952	M	W	4	0	17	Priest	.....	110	110	240	NPH 70
Normal	None	.....		11/14/30	1950	F	W	1	Toxemia of pregnancy	14	.....	Married 1 child	85	100	175	C 38 P 40
Normal	Right posterior tibial	.....		.....	1952	...	...	1	.....	.....	.....	Married 1 child	85	100	175	C 38 P 45
Normal	None	.....		3/24/27	1950	M	W	0	0	17	Dry cleaning	Married 2 children	95	95	195	C 30 P 15
Normal	Posterior tibials	.....		.....	1952	...	...	0	0	.....	Popcorn salesman	Married 2 children	95	95	195	C 25 P 12
Normal	None	.....		1/21/35	1950	M	W	0	0	15	School	.....	146	145	254	C 20 P 37
Normal	None	Marked on feet		10/24/34	1952	F	W	0	0	13	.....	Married	80	100	220	C 32 P 45
Normal	None	.....		11/11/24	1950	F	C	0	Syphilis (acquired)	16	Maid	.....	90	105	110	C 18-0-C 18 P 70
Normal	None	.....		6/ 4/37	1950	M	W	2	0	.....	School	.....	95	85	220	C 14 P 18
Calcified area left mid-lung	None	.....		8/25/34	1952	M	W	0	0	15	Shoe factory	.....	110	105	270	NPH 65
Normal	None	Moderate on feet		7/25/29	1951	F	W	0	0	16	Shirt factory	.....	80	115	210	C 30 P 64
Calcified glands left upper mediastinum	Dorsalis pedis rt.	Three tiny spots on feet		10/13/26	1951	M	W	0	0	14	Clothing store	Married 1 child	130	125	266	C 32 P 48
Calcified glands left upper mediastinum (healed med. Tbc.)	Tibial arteries	.....		.....	1952	...	...	0	0	.....	Clothing store	Married 1 child	130	125	266	C 32 P 48
Normal	None	.....		6/20/32	1951	M	W	0	0	18	Office work	.....	100	85	255	C 16 P 38
Normal	None	.....		1/21/36	1952	M	W	0	0	16	School	.....	100	75	180	C 40 P 40
Normal	None	Marked on feet; moderate legs to knees		7/22/24	1951	F	W	0	Emotional instability	13	.....	Just married	95	120	180	C 36 P 68
Increase root infiltration (non-specific)	None (Phleboliths)	.....		12/27/29	1950	F	W	0	0	14	.....	Married (2 children since survey)	100	85	200	C 20 P 55
Normal	None	.....		10/12/37	1952	M	C	0	Allergy	15	School	.....	120	100	250	C 45 P 55
Normal	None	.....		3/14/37	1952	M	W	0	0	.....	School	.....	110	110	250	C 15 P 15
Normal	None	Spotty on feet and right calf		3/11/28	1951	M	W	1	0	16	Attendant State Hospital	Married	120	150	180	C 20 P 35
Small area calcification rt. hilum	None	.....		.....	1952	...	...	1	0	.....	Attendant State Hospital	Married	100	100	200	NPH 55
Left lung collapsed (oleo-thorax)	None (Phleboliths)	.....		9/ 1/22	1950	F	W	2	Pulmonary tuberculous (healed)	15	Secretary	.....	85	70	150	C 26 P 64

MISCELLANEOUS DATA

meet the situation. Those who fall short of this ideal at this stage of their development are for the most part those in whom early efforts at training have failed through ignorance, lack of parental cooperation, poor home situations, irregularity in clinic attendance, or general carelessness. Many of these are the patients who keep appearing on the adult wards in trouble where they create the mistaken impression that juvenile diabetes inevitably carries with it a gloomy prognosis.

Three years ago, a survey of those clinic patients who had had their disease for ten years or more was begun with reference to vascular complications, chiefly retinal and renal. The purpose of the study was, first, to determine the incidence and the time of appearance of these complications and, second, to determine whether there was a correlation between the occurrence of complications and the extent to which the diabetes had been controlled. The survey included, in addition to general physical examination, detailed ophthalmoscopic examinations, urinalyses and kidney function tests, x-ray studies of the legs for evidence of calcification in the arteries, and blood cholesterol determinations, with a few other miscellaneous observations.

Of patients qualified for such analysis, forty were available for study and the results are summarized in the accompanying tables. More than a third of the patients, who were among the first to be surveyed, have since been re-evaluated. Only the results of the latest survey are included in the tables, except in those few in whom a change has taken place. Several, who were checked for future reference at the beginning of the study when still at the eight- or nine-year level and who have since passed the ten-year mark, have been resurveyed for inclusion in the study. All of the patients, except during absences from the clinic when living out of town and during admissions on the adult wards when in trouble, after passing the age limit for admission to the pediatric wards, have been under the observation of the same physicians. Hence clinical observations and conclusions, though subject to human error, are based on uniform criteria throughout, supplemented by intimate knowledge of the individual. Ophthalmological and x-ray reports are wholly objective since the ophthalmologist who surveyed the fundi and the radiologist who interpreted the x-rays knew nothing of the clinical status of any of the patients at the time of their examination.*

With very few exceptions, the patients under consideration have shown normal growth and development, having matured within normal age limits, are in relatively good physical condition despite the abnormal findings noted and are leading lives that are in keeping with their age, their intellectual and emotional endowment and their family and other environmental circumstances. Because of variations in their diabetic status at different stages of the disease, the course of each has been divided into five-year periods and the measure of diabetic control during each period has been graded separately as *good*, *fair*, or *poor*. In those in whom the duration has exceeded fifteen years, the third five-year period reflects the degree of

*We are indebted to Dr. William Marr of the Wilmer Eye Clinic and Dr. David Gould of the Department of Radiology for the special studies mentioned above.

control thereafter, since by then the pattern has been well established. While in some the level has declined with the passage of time, in a few there has been improvement as a result of better understanding of their disease or the development of a sense of responsibility initiated by the necessity for earning a living for themselves or supporting a family.

For evaluation of the degree of control, criteria have been made as objective as possible, although personal knowledge of the patient has added a modifying factor. From the objective standpoint, *good* control implies (1) careful adherence to diet, (2) glycosuria not in excess of reasonable limits (20 grams ± daily), as determined on clinic visits and by records kept at

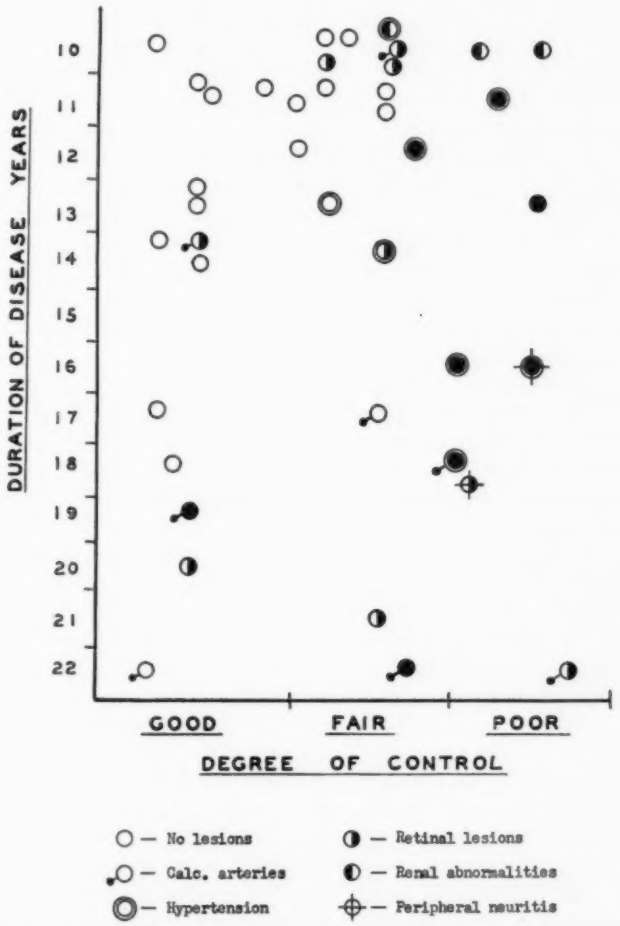

Fig. 1.—Graphic representation of abnormalities in relation to degree of control and duration of diabetes at time of survey.

home, (3) no episodes of severe acidosis or coma (acidosis at onset and the occasional mild acidosis, promptly and readily controlled, that may accompany infection are excepted), (4) stability of diabetic status, (5) good adjustment to the diabetic way of life, and (6) regularity of habits in general, including regularity in attendance at clinic or in acceptance of medical supervision elsewhere; *fair* control indicates (1) fair adherence to general dietary principles outlined but with regular indulgence in extras such as candy, cake, cookies, soft drinks, etc., (2) glycosuria usually in excess of reasonable limits, (3) episodes of severe acidosis or coma only infrequently, and (4) diabetic status stable with, however, (5) some irregularity in habits, including haphazard clinic attendance; control is rated as *poor* when there is (1) no adherence to a suitable dietary regime, (2) excessive glycosuria at all times or fluctuations between periods of excessive glycosuria and episodes of hypoglycemia, (3) frequent hospitalizations for severe acidosis and coma, (4) unstable diabetic status, and (5) poor adjustment to the needs and demands of a diabetic career.

Since not all of the patients meet all of the criteria established for one particular group, it has been necessary, in the tables, to qualify some of the grades by + or – signs, in order to indicate that the individual is more or less well controlled than the average for that group and in order to establish a basis for estimating the patient's over-all status for the total duration of his disease, when all of the periods are considered together. In Fig. 1, each grade of control is represented by a zone. With each patient placed in the appropriate section of the zone to which his average relegates him, the general grouping is graphically presented in terms of both duration and control, and certain trends are at once apparent.

In the final analysis, there are fourteen patients whose control can be rated as *good;* seventeen in whom it is *fair,* and nine in whom it is *poor.* While these groups are too small for absolute statistical analysis, the facts that emerge are highly suggestive in demonstrating that the degree of control, as well as duration of disease, plays an important role in the development of vascular complications. These facts may be summarized as follows:

1. Of fourteen patients whose control has been consistently *good* throughout, only four show the designated abnormalities after thirteen to twenty-two years of disease. One of these (No. 23) has moderate calcification in the tibial vessels as the only finding and another (No. 40), after surviving an extensive pulmonary tuberculosis with cavitation, only minimal changes in the retinal vessels. The third (No. 24), with more pronounced changes in all fields, had experienced a severe toxemia of pregnancy just a few months before the first survey. In the fourth (No. 32), only thirteen years after onset, there is a moderate degree of retinitis, and there is calcification in the arteries of the legs, which has increased only slightly during the one year since the initial survey.

2. Of seventeen patients whose control is *fair,* ten show changes after ten to twenty-two years of disease. Those in the upper zone have fewer abnormalities than those in the middle and

lower zones. In one of these (No. 28) there is only hypertension, which may not be directly attributable to the diabetes, since the patient comes from a hypertensive family. While several others present only minor changes, there is a distinct increase in the incidence of multiple findings in this group.

3. Of nine patients with *poor* control, none has escaped complications after ten to twenty-two years and in the majority these are multiple. Two show advanced irreversible changes in the retinae. The two who are free of retinal lesions have only just reached the ten-year level. All but two show definite renal abnormalities and four have hypertension in addition to other findings. In one of the patients (No. 4), who has had the disease for the longest period of time and whose growth and sexual development have been impaired by years of poor control, vascular lesions are surprisingly mild.

4. In terms of *duration*, twelve, or less than half of the twenty-seven pa-

TABLE II. ABNORMAL FINDINGS IN RELATION TO DEGREE OF CONTROL

	DURATION OF DISEASE (YR.)	RETINITIS	RENAL FINDINGS				CALCIFICATION	HYPERTENSION	MISCELLANEOUS
			ALB.	R.B.C.	PSP LOW TOTAL	PSP FLAT CURVE			
Good 4/14									
Nos. 32	13	++					+		
24	19	++	+				+		
40	20	+							
23	22						++		
Fair 10/17									
Nos. 5	10				+	+		+	
15	10	+					+++		
36	10	+	+	+					
38	10	+							
13	12	+	+		+			+	Cholesterol 420 mg. %
28	13							+	
20	14	+					+	+	
25	17						++		
17	21	++							Vitreous hemorrhage
6	22	+++	+			+	++		
Poor 9/9									
Nos. 10	10		+						
37	10				+				
30	11	+	+					+	
31	13	++	+						
8	16	+++			+			+	
35	16	++++	+					+	Peripheral neuritis
9	18	++++	+	+			++	+	Cholesterol 434 mg. %
39	18	+							Peripheral neuritis
4	22	+					++		Delayed puberty

Gradation of retinal lesions:
+ occasional aneurysm.
++ moderate number of aneurysms.
+++ aneurysms and exudates.
++++ aneurysms, exudates, and proliferative changes.

PSP low if total 2-hour excretion is less than 60 per cent, unless there is at least 40 per cent in first half hour.

Calcification in arteries:
+ barely discernible.
++ more definite but limited to one or two vessels.
+++ marked and in several vessels.

As criteria for hypertension, a systolic pressure consistently above 125 and a diastolic above 80 were arbitrarily chosen.

tients still in the first fifteen years of their disease, show abnormalities, while only two of the thirteen who have passed the fifteen-year mark have escaped completely. It is noteworthy, however, that, of the patients with *good* control, only one shows changes in less than fifteen years, while two are still completely clear after seventeen and eighteen years, and two others show only minimal changes after as long as twenty and twenty-two years. In the *fair* group, seven or exactly half of the patients below the fifteen-year level and all beyond it show abnormalities, while in the *poor* group, as already indicated, not one is clear at any level. In both the fair and the poor groups, there is a disturbing number of patients barely past the ten-year mark who are already showing changes.

5. *Retinal changes*, which are the most specific, are also the most outstanding in all groups. In several patients in the poorly controlled group, these are extreme and irreversible; in most of the remainder the retinitis is only mild to moderate in degree. Lenticular opacities, described by the ophthalmologist in a few patients, are said not to be of diabetic origin.

6. *Renal abnormalities*, which are next in order, are not measurably far advanced in any. Albuminuria is the most frequent of these, although, in one patient in the *fair* and one in the *poor* group, a few red blood cells also have been demonstrated. A reduction in total phthalein excretion or a flat curve of excretion has been demonstrated in three patients in the *fair* and two in the *poor* groups. There is no clinical means of determining whether the abnormal findings referable to the urinary tract are specifically related to the diabetes or whether they are coincidental. In those patients with associated retinal lesions, the presumptive evidence is, however, good.

7. *Calcification in the arteries* of the legs is demonstrated about equally in all groups. In one patient it is the only abnormal finding, and in only one are the lesions really striking. Without similar observations in a nondiabetic group of patients of comparable ages, the significance of this is uncertain.

8. *Hypertension* of moderate degree is present in eight patients, equally divided between those with *fair* and those with *poor* control. In No. 28, previously referred to, with a family history of hypertension and no other abnormal findings, the relationship of the hypertension to the diabetes is open to question. In all of the others, however, the presence of both retinal and renal abnormalities makes it likely that the associated hypertension is significant.

9. Sporadic *cholesterol* determinations have given readings above 300 mg. per cent in nine patients. In three of these there are no other findings and control is good or fair. Since values of 300 mg. per cent or more have been reported from this laboratory in patients without diabetes or other obvious reason for an elevation, no emphasis can be placed on readings at this level. Levels of more than 400 mg. per cent, noted in two patients, can, however, be regarded as definitely beyond the normal range. Both of these are patients in whom there are multiple abnormalities. One is the patient with hyperthyroidism, successfully treated with propylthi-

ouracil, whose basal metabolic rate now is normal. Other factors may be operating here.

10. *Skin resistance* tests, that were done on a few of the patients, have shown abnormalities which are as yet of uncertain significance. These patients are members of a study group to be reported later by Dr. Curt Richter, who kindly consented to inclusion of the data in the tables for future interpretation and correlation with other findings.

11. Of *miscellaneous factors,* such as *sex, age at onset, year of onset* (as it reflects the type of diet and insulin used), *other chronic diseases* experienced, etc., that may play a role in the outcome, only the *age at onset* (Table III) is of suggestive significance. Half of the twenty patients in whom diabetes began during the preschool period are well controlled, while there is a gradual decline in the incidence of good control as the age at onset advances toward puberty. Furthermore, the majority of the well-controlled patients (ten out of fourteen) are those in whom the diabetes started during the first five years of life. This is the age at which training is most successful and good habits most easily established. By the time these children reach the age of 10 or 12, when temptation is greatest, they have followed the routine so long that they remember no other way of life.

From these observations, which are in agreement with those reported from other clinics as a result of similar studies, one cannot escape the conclusion that *poor* control of diabetes favors the early development of vascular changes. Furthermore, in the poorly controlled group, changes tend to be more severe and more rapidly progressive than in those patients whose regulation has been maintained continuously at a satisfactory level. Whether persistently higher levels of blood sugar, more frequent episodes of acidosis, less adequate diets or possibly even less careful attention to general health and foci of infection in the presence of diabetes are responsible singly or in combination, one cannot say in our present state of knowledge. With the evidence that *good* control can, however, both postpone and lessen the severity of degenerative changes, it is imperative that every effort be made to achieve and maintain as good control as is humanly possible in all children with diabetes, while endeav-

TABLE III. DEGREE OF CONTROL IN RELATION TO AGE AT ONSET

AGE AT ONSET (YR.)	GOOD	FAIR	POOR	
1	2	1		
2	2	1		
3	3	1	1	
4	2	2		
5	1	3	1	Total 20
6		1	1	
7	1		2	
8	1	1	1	
9	1	1		
10			1	Total 11
11	1	1		
12		4	2	
13		1		Total 9

oring at the same time to guard their general health and to make of them normal, well-adjusted individuals with a psychologically healthy attitude toward their disease. With the intelligent patients, the problem is not a difficult one, if the physician himself recognizes his responsibility in bringing this to pass and leads the way. With the less intelligent or those whose background promotes a casual, haphazard attitude, the problem is ever pressing. For them, frequent clinic visits at regular intervals, fostered by social service follow-up and assistance in the everyday problems at home, which may extend far beyond the implications of the diabetes itself, are especially important and may, in many instances, determine the patient's ultimate course. Certainly the philosophy of the free diet, which encourages a more casual attitude toward his disease, may be a dangerous one for the child or young adult who is destined to spend his life with diabetes.

CONCLUSIONS

1. Vascular complications of diabetes, especially those that can be detected in the retina, may be found relatively early in the course of juvenile diabetes.

2. While the incidence of such complications increases with the passage of time, the time of appearance, severity of lesions, and rapidity of progression are modified by the degree of diabetic control.

3. Patients with only *fair* or *poor* control may show lesions as early as ten years after onset and rarely escape some evidence of vascular damage by the time the disease has been in progress for fifteen years.

4. Patients consistently *well controlled* may remain free of lesions for as long as eighteen years and may show no more than minimal changes of doubtful significance as long as twenty-two years after onset. Even in those who do not escape completely, the first appearance of lesions is delayed and the lesions are less rapidly progressive than in the other groups.

5. In children in whom the onset of diabetes occurs during the preschool period, good control is more easily established and maintained than in those in whom it occurs at a later date, when habits are more fixed and there has already been a taste of freedom. Accustomed to parental guidance during the early years they adjust more easily to the few limitations imposed by diabetes and soon remember no other way of life.

6. As good control as can reasonably be achieved should be the goal in the treatment of all patients with diabetes at all ages.

7. Regularity of attendance at clinic or the physician's office, which permits careful supervision and systematic training in the diabetic way of life, is an important factor in the maintenence of good control. Attention to general health and habits is also of importance.

8. Adequate social service assistance is an essential adjunct to a diabetic clinic if the goal of satisfactory regulation, so essential to their future health, is to be achieved in the greatest possible number of patients.

SUMMARY OF CASES

CASE 1.—H. C., born June 20, 1924, was first admitted to the hospital in the early spring of 1928 with the typical symptomatology of diabetes. There

were three siblings living and well, and the family history was negative for diabetes. After a long hospital stay, complicated by otitis media, mastoiditis, and mastoidectomy, he was discharged without insulin, as was sometimes the custom in the early days of insulin therapy after regulation was achieved, on a diet supplying 100 Gm. of carbohydrate. By the end of a year of haphazard supervision, with frequent infections and a rapid decline in carbohydrate tolerance to 30 Gm. daily, his family, at first opposed, finally consented to another admission for re-regulation and insulin therapy. By now ketosis was consistently present, even when the urine was sugar-free, and the child was fatigued by a walk of only a few blocks. There had been an increase in height of only one inch during this first year.

After three weeks in the hospital, during which infected tonsils and adenoids were removed and there was a gain in weight of 5 pounds, the patient was discharged, still in the shadow of the ketogenic-antiketogenic era, on a diet that supplied only 65 Gm. of carbohydrate, with a regular insulin dosage of 9 units before breakfast and 7 units before supper. A year later, he joined the newly formed diabetic clinic. Attendance, previously haphazard, now became more regular and his course more steady, although there were still many infections, rather frequent dietary transgressions, in spite of a gradual increase in the allowance of carbohydrate, and other irregularities in his routine due to the fact that his mother was forced to work because of an alcoholic father's failure to support the family. During this period, growth was better, with an increase in height of 10 inches during the first five years of insulin treatment, and psychometric examination demonstrated an intelligence quotient of 99.

In 1935, when the patient was just 11, the mother and children moved to a small town in Ohio to escape the alcoholic father. By then the diet had been modernized to supply 170 Gm. of carbohydrate and was controlled by a daily insulin dosage of 16 units before breakfast, 10 units before lunch, and 20 before supper. Shortly after their arrival in Ohio, there was an episode of acidosis following which the attending physician decreased the carbohydrate in the diet to 100 Gm. and told the mother that the boy probably would not live to reach adult life. A year later the family moved to Pittsburgh, where the patient again experienced frequent severe infections which necessitated many hospital admissions for treatment of acidosis. In the course of these he was restored to a more liberal diet, but he failed to attend clinics or to submit to regular medical supervision between hospitalizations. On one such admission, he was placed on protamine insulin. Shortly thereafter, because of several severe reactions, he discontinued the protamine and resumed treatment with regular insulin on his own, taking four doses a day, and eating as he pleased, although perhaps roughly approximating the dietary limits to which he was accustomed. There was again a slowing of growth such that he had achieved a height of only 56 inches by the age of 16. This represented a growth of only 5 inches during the five years since he had left the clinic. At about this time the alcoholic father died.

In 1950, fifteen years after his departure from Baltimore, this boy, returning to seek a living here, suddenly reappeared in the Harriet Lane Diabetic Clinic. The account of his career during his long absence was very revealing. Quite honest in his self-evaluation, he admitted that his regulation of himself had been far from satisfactory. Wide swings in blood sugar had apparently accounted for difficulties in school, as he had often been drowsy and confused in the afternoons, no doubt from hypoglycemia. Yet he had rarely sought medical assistance. A delay in the onset of puberty had also complicated the picture. At 18 years, he had left

school, partly because his poor concentration during hypoglycemic periods interfered with satisfactory performance and partly because the boys made fun of his juvenile habitus. After a few more years, during which a few signs of puberty finally did appear, he had consulted a doctor who, instead of trying to improve his diabetic control, had given a course of treatment with methyl testosterone. Meanwhile he had made no effort to follow any careful dietary regime although there was some constancy in the type of diet selected. As outlined by him, this proved to be not only excessive in carbohydrate content but grossly deficient in protein. Lacking enough money to buy both milk and cigarettes, he had formed the habit of omitting the former in favor of the latter.

This boy's timely arrival made it possible to include him in the survey while steps were taken to improve his regulation and the quality of his diet. On the insulin dosage of C25-10-15-5, prescribed by himself, blood sugars ranged from a high fasting level of 454 mg. per cent to hypoglycemic levels of 56 mg. per cent in the mid-afternoon. Short of stature (his height was now 61½ inches) and still lacking a beard, he was referred to the Endocrine Clinic, where adult sexual development was demonstrated in spite of the lack of beard, and where it was determined that his slow growth and delayed development could be wholly accounted for by hereditary and constitutional factors in combination with years of poor diabetic control.

After a few months of sporadic attendance at the clinic, during which there was enough improvement in control to permit an enlarged liver to recede to normal dimensions but before the boy could be induced to accept hospitalization for more thorough regulation, he disappeared as suddenly as he had come. This patient, never under supervision long enough for adequate orientation and education in the management of his disease, but with enough pseudo-knowledge to make him feel that he could manage himself, is truly adrift on the sea of diabetes, poorly adjusted, immature, and seeking security in a long outdated regime that, to him, though poorly understood, probably reflects the only period of security that he has known.

While vascular changes, as evidenced by the diabetic retinitis noted in the survey, are of only mild degree, stunted growth, delayed puberty, and a greatly distorted outlook on life are additional consequences of a diabetic career not only poorly controlled but also unsupervised and far removed from the educational regime to which even the least cooperative patients who attend clinic with any degree of regularity are exposed. Sporadic blood sugar determinations and urinalyses, in the course of observations here, demonstrated at least that hyperglycemia was not continuously present and that there was no acidosis during periods of freedom from infection.

CASE 2.—J. M., born March 20, 1927, was admitted to the hospital on Dec. 11, 1929, for regulation of diabetes which had been diagnosed following investigation of a complaint of urinary frequency. There were three siblings, all living and well, and the family history at that time was negative for diabetes. Three years later, however, a 14-year-old maternal aunt developed diabetes; shortly, thereafter, a maternal uncle, also in his teens, followed suit. In the meantime, two more siblings were born. The first of these, now 19 years of age, developed diabetes at the age of 12, and, in 1951, the 10-year-old daughter of the diabetic aunt brought the final family total to five.

After a month in the hospital for initial regulation, the patient was discharged on a diet, typical of the era, which supplied 65 Gm. of carbohydrate, with an insulin dosage of 7

units before breakfast and 5 units before supper. At home, his conscientious, intelligent mother followed directions so carefully that the urine was practically sugar-free most of the time. In fact, it was kept so clear that the slightest variation in the child's activity, such as omission of his afternoon nap, resulted in insulin reactions. There were rather frequent infections during these early years, which necessitated tonsillectomy in 1931 and which were responsible for hospital admissions, mainly because of associated vomiting and diarrhea with mild degrees of acidosis, requiring therapy with intravenous fluids. At no time, however, was there an episode of severe acidosis and the boy has never been in coma.

In December, 1936, the patient was shifted to protamine insulin. Then on a diet supplying 150 Gm. of carbohydrate, with regular insulin before each meal (15-8-9), he was adjusted on 14 units of protamine and 5 units of regular insulin before breakfast. Three months later, at the insistence of the mother, protamine was abandoned in favor of the old routine. Accustomed to the greater flexibility in the use of regular insulin and the greater uniformity in the effects of a given dosage, she was frustrated by the irregularities characteristic of the protamine regime and the need for allowing a reasonable degree of glycosuria. In the summer of 1938, however, after a winter during which frequent infections complicated his course, the mother consented to resumption of protamine therapy. The diet, now supplying 185 Gm. of carbohydrate, was covered by 14 units of protamine and 10 units of regular insulin, and the protamine regime was continued thereafter without interruption. There was a gradual increase in diet to a final level of 220 Gm. of carbohydrate and an insulin dosage of 37 units of protamine with 17 units of regular insulin by the time puberty was established. A shift to NPH insulin with a few alterations in diet has been made elsewhere within the past year.

This boy, well adjusted to the diabetic way of life by the time he entered school and by nature conscientious and intelligent, has never presented any problem in cooperation and his regulation has been maintained at a highly satisfactory level, with only minor interruptions, at all times. At the age of 10, he was quite disgusted with the aunt and uncle who, in their late teens, made no effort to follow any rules. At the age of 12, on reading a magazine article in which a 20-year-old boy, just discovered to have diabetes, had written a long lament, with the conclusion that life was no longer worth living, the patient worded an indignant reply, stating that the boy did not know what he was talking about, and insisting that adherence to a reasonable diet and daily injections of insulin imposed no hardship. By the time he reached high school, he was completely self-sufficient, choosing his own diet without the use of scales, and attending occasional parties at which he judiciously partook of refreshments, adjusting his insulin dosage accordingly.

After his father's death in 1943, the patient left school to help support the family, finally entering the priesthood when his help was no longer needed. His period of training has just been completed and he now travels extensively in the performance of his duties, often far removed from the possibility of medical supervision. His survey, completed within the past few months, has revealed no significant abnormality after twenty-two years of the disease.

Meanwhile, the diabetic aunt, who had so aroused this boy's indignation by her carelessness and her refusal to submit to any dietary restrictions in the early years of her disease, has died of chronic nephritis. Her course was characterized by one hospital admission after another in severe acidosis, with a diabetic retinitis first noted at

least ten years before her death. Unfortunately, while presumptive evidence was good, there was no autopsy to determine whether the renal lesions were those of Kimmelstiel-Wilson's disease.

CASE 3.—C. D., born June 26, 1927, the son of a fireman, was seen first on May 5, 1930, when typical symptoms of diabetes of several weeks' duration brought him to the hospital. There were two siblings living and well. Except for a history of diabetes in the maternal grandfather late in life, the family history was and has remained negative. Regulation was accomplished with relative ease and he was discharged on a diet supplying 100 Gm. of carbohydrate with 2 units of insulin before each meal, shortly thereafter increased to 8-4-5.

This boy's mother, cooperative but of limited intelligence, made frequent mistakes through lack of understanding. While no serious episodes of acidosis resulted, there was considerable irregularity in the state of the child's control with fluctuations between too much glycosuria and hypoglycemia and with frequent hospital admissions for readjustment and for treatment of his many infections. In 1931, the tonsils and adenoids were removed and in 1932 there was an episode of catarrhal jaundice that appeared to leave no sequelae. The boy himself, also of limited intelligence, played a passive role in the regulation of his diabetes, submitting to the restrictions imposed but making no great effort to understand or manage his disease or to resist temptation when it crossed his path.

In December, 1936, with J. M., he was admitted to the hospital for a shift to protamine insulin. He has since remained on this regime without interruption, in spite of early irregularities which did not disturb him or his less exacting mother. Just before the change, his diet supplied 170 Gm. of carbohydrate with an insulin dosage of 16-5-10. With an increase in carbohydrate to 185 Gm., the final insulin dosage, after the change, amounted to 20 units of protamine with 10 units of regular before breakfast.

Until 1942 this boy attended clinic regularly, following his diet fairly well, but not hesitating to eat extras when he wished, and still experiencing rather frequent infections. Recurrent adenoids were treated with radium in 1939. In 1940, an eye examination demonstrated a refractive error but the fundi were described as completely normal. A psychometric examination during this same year, requested because of poor progress in school, yielded an intelligence quotient of 100, although the boy had barely passed into the sixth grade at 13 years.

In 1943, after a year's absence from clinic, the patient was admitted on the adult medical service in moderate acidosis precipitated by an ear infection. By then, the carbohydrate content of his diet had reached 240 Gm. and he was receiving 50 units of protamine insulin with 30 units of regular insulin daily. For six months after this, he attended clinic regularly once more with consequent temporary improvement in his diabetic status. Then there was another long absence during which he left school to work in the shipyards and became more careless about his diet. In 1945 and 1946 there were again several visits, initiated by requests to return, but since 1946 the patient has been seen only twice. These were the two occasions (in 1950 and 1952) on which he was asked to return for survey. In the meantime, he had married, at the age of 19 years, and now has two children. There has been no need for hospitalization since 1943, but he admits that he rarely examines his urine and that he takes foods not legitimately included in his diet, when the spirit moves, although his wife is careful in the management of meals supplied to him at home. While his general condition is good and physical examination reveals no gross abnormalities, retinal changes are advanced and other complications are also making their appearance.

REFERENCES

1. Dolger, Henry: Clinical Evaluation of Vascular Damage in Diabetes Mellitus, J. A. M. A. 134: 1289, 1937.
2. Guest, G. M.: Unrestricted Diet in the Treatment of Juvenile Diabetes, J. Am. Dietet. A. 23: 299, 1947.
3. Lichtenstein, A.: The Management of Childhood Diabetes, Bull. Schweiz. Akad. d. med. Wissensch. 3: 97 (Dec.), 1947.
4. White, Priscilla, and Waskow, Eleanor: Arteriosclerosis in Childhood Diabetes, Proc. Am. Diabetes A. 8: 141, 1948.
5. White, Priscilla: Free vs. Controlled Regime in Juvenile Diabetes, J. Am. Dietet. A. 25: 757, 1949.
6. Jackson, Robt. L., Hardin, Robt. C., Walker, Glenn L., Hendricks, Atlee B., and Kelly, Helen G.: Degenerative Changes in Young Diabetic Patients in Relationship to Level of Control, Pediatrics 5: 959, 1950.
7. Root, Howard F., Sinden, Richard H., and Zanca, Ralph: Factors in the Rate of Development of Vascular Lesions in the Kidneys, Retinae and Peripheral Vessels of the Youthful Diabetic, Am. J. Digest. Dis. 17: 179, 1950.
8. Daeshner, C. Wm., Deisher, Robt. W., and Hartmann, Alexis F.: Later Status of Juvenile Diabetics, J. PEDIAT. 38: 8, 1951.
9. Wilson, J. L., Root, H. F., and Marble, A.: Prevention of Degenerative Vascular Lesions in Young Patients by Control of Diabetes, Am. J. M. Sc. 221: 479, 1951.
10. Sherrill, James W.: Diabetic Retinitis; the Relationship Between Retinal Degenerative Changes and the Degree of Diabetic Control, Bull. Scripps Metabolic Clinic 2: 1 (Oct.), 1951.
11. Wilson, James L., Root, Howard F., and Marble, Alexander: Controlled Versus Free Diet Management of Diabetes, Diabetes 1: 33, 1952.
12. Marr, Wm. G.: Cataracts and Retinopathy in Juvenile Diabetics, Am. J. Ophth. 35: 577, 1952.

BRONCHIAL OBSTRUCTION AND BRONCHIECTASIS COMPLICATING PRIMARY TUBERCULOUS INFECTION

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BRONCHIECTASIS has long been recognized as a complication of various acute respiratory infections, where a combination of atelectasis and infection is present. Pertussis, measles, and pneumonia (probably in most instances of virus etiology) are the most common precursors of this disease. It is only within recent years that bronchiectasis has been recognized as a sequela of primary tuberculous infection.

Brock and his co-workers[3] were among the first to suggest that bronchiectasis might follow mediastinal lymphadenitis of tuberculous origin in patients where bronchial obstruction was present, and where roentgen examination showed pulmonary shadows compatible with "epituberculosis." Hughes and Simpson[6] reviewed the literature on this subject and discussed tracheobronchial obstruction from enlarged lymph nodes. Kent[9] reported the occurrence of bronchiectasis in seven of ten patients with atelectasis resulting from primary tuberculous infection. All seven patients had evidence of bronchiectasis within twenty months of the time at which the atelectatic process was first recognized and one patient in six months.

Jones, Peck, and Willis[7] reported on thirty-seven children with known obstructive tuberculous lesions followed for three and one-half years; bronchograms done on thirty-four of these children showed bronchiectasis in twenty-four. These authors point out that endobronchial tuberculosis is a frequent complication of primary pulmonary tuberculosis and may play a role in the production of obstruction. In a subsequent article[8] the authors suggest that the bronchiectasis associated with primary tuberculous infections tends to be co-extensive with the bronchus and of the cylindrical type from root to periphery. In their series the disease was found most frequently in the anterolateral (pectoral) segment of the upper lobe (nine cases), in the apical segment of the lower lobe (four cases), and in the right middle lobe (four cases). These authors also present observations made on patients with reinfection pulmonary tuberculosis; autopsy material was studied both by injection with radiopaque substance and by the examination of histologic sections. By these methods bronchiectasis was found in 50 per cent of the fatal cases. Where bronchiectasis was present the bronchi which were dilated were actually the seat of tuberculous disease.

This report includes: (I) observations derived from the study of thirty-five patients, all of whom have, or have presented in the past, evidence of bronchial obstruction complicating primary pulmonary tuberculosis; and (II) observations derived from the

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autopsy protocols of 186 tuberculous children.

I. The observations made on the patients consist of serial roentgenograms of the chest, bronchoscopic examinations, bronchograms, and, where surgery was performed, examination of the surgical specimen. These observations were made in addition to the routine diagnostic examinations.

The patients studied have been examined, in most instances, both by bronchoscopy and bronchography done with local anesthesia (pontocaine 0.5 per cent) following sedation with Nembutal (sodium pentobarbital) orally and morphine sulfate subcutaneously. An iodized oil, Iodochlorol, was used as a contrast medium for bronchography, injected through a soft rubber catheter passed into the trachea. Bronchograms were usually done one to seven days after bronchoscopy and whenever possible the configuration of all five lobes was outlined during one examination. No untoward reactions were encountered. In no instance was a general anesthetic required. As will be seen below there were several patients on whom only one type of examination (either bronchoscopy or bronchography) was carried out.

In all, thirty-five patients have been studied. Twenty-nine of the thirty-five patients were bronchoscoped and twenty-eight were bronchogrammed. There were seven patients submitted to bronchoscopy on one or more occasions on whom bronchograms have not yet been done because of the recent onset of symptoms and signs of obstruction. These patients will be examined by bronchography when the acute phase of the tuberculous process has subsided. Six of the thirty-five patients were not examined bronchoscopically even though bronchograms were done. The bronchoscopic examinations were not done because of unwillingness on the part of the patient or parents. In all of these patients the tuberculous process was known to have been inactive for at least five years. Twenty-two patients have been examined by both bronchoscopy and bronchography. The twenty-eight patients who have been examined by bronchography have been under observation an average of 8.9 years (range six months to twenty-five years).

II. While the autopsy protocols on 186 children dying of tuberculosis between Jan. 1, 1928, and Dec. 31, 1940, were being reviewed for another purpose it was noted that bronchiectasis was described in fifteen instances. The cause of death in these fifteen patients was listed as tuberculous meningitis in ten, miliary tuberculosis in one, severe tuberculous pneumonia in one, and superimposed overwhelming pulmonary infection due to secondary bacterial invasion in three.

OBSERVATIONS

I. *Bronchial Obstruction.*—Evidence of bronchial obstruction complicating primary tuberculous infection was found in the following ways:

1. Of the twenty-nine patients bronchoscoped eleven had evidence of partial or complete bronchial obstruction. In ten of the eleven patients endobronchial tuberculous lesions were present, in eight of these the lesions were still active, and in two they were represented by scarring and stricture. Where the lesions were active they consisted of heaped up granulation tissue (see Fig. 1, *D*), hypertrophy, reddening, and edema of the mucous membrane. Four of the eleven patients

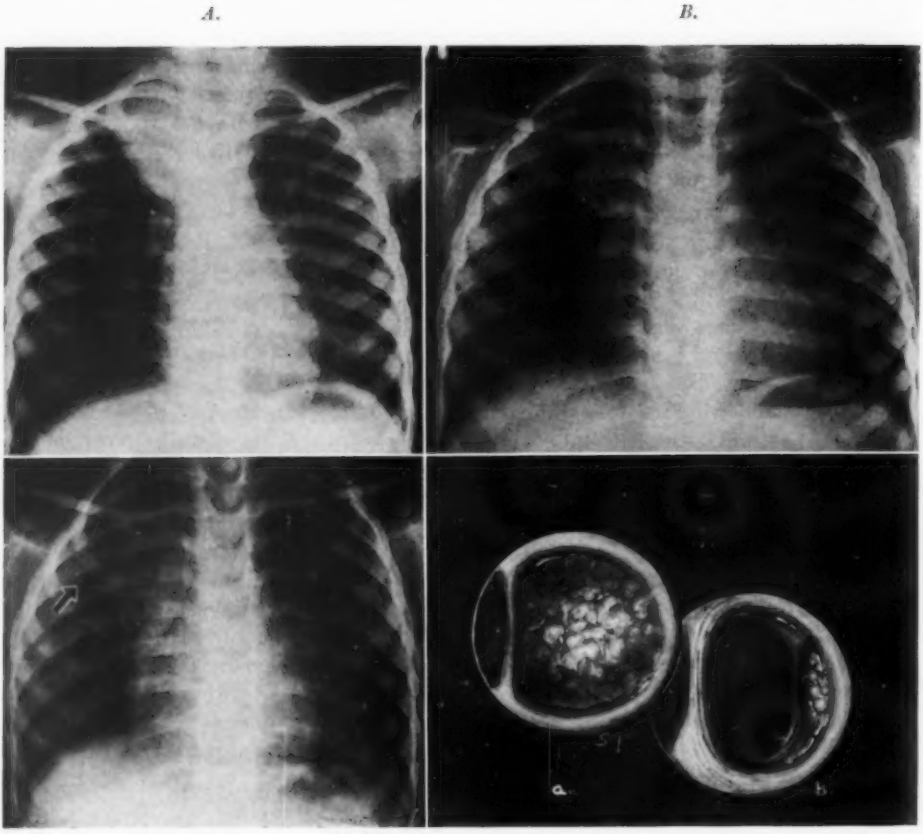


Fig. 1.—H. L., a Negro male, aged 2½ years.

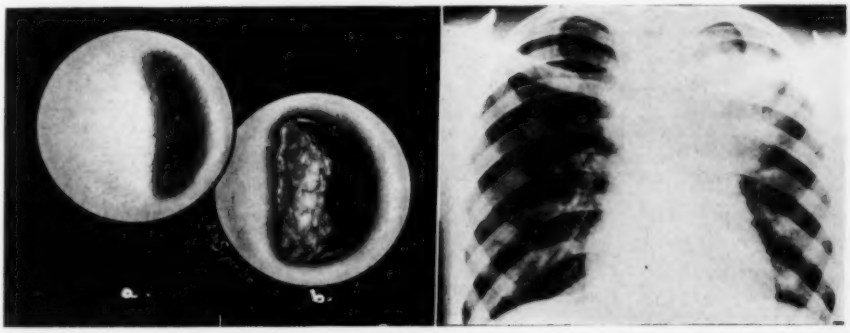
A, Chest film shows a dense triangular shadow at the right apex produced by marked atelectasis of the right upper lobe. Bronchoscopic examination demonstrated endobronchial tuberculosis with plugging of the right upper lobe bronchus with tuberculous granulation tissue which extended down into the main bronchus for about 1 cm.

B, Chest film nine days after that shown in *A*. During this period two bronchoscopic examinations were done with removal of a large amount of granulation tissue, which proved microscopically to be tuberculous. The right upper lobe was partially re-expanded. A six-week course of streptomycin was started after the first bronchoscopic examination.

C, Chest film six weeks after that shown in *B* shows further expansion of the right upper lobe. The arrow indicates the fissure between the upper and middle lobes which is still somewhat elevated. Enlargement of the bronchial nodes on the right persists with increase in the width of the mediastinal silhouette. No parenchymal disease is evident. Bronchography showed only partial reduction in volume of the lobe.

D, The drawing *a* depicts the right main bronchus as seen through a 4 mm. bronchoscope (just after the x-ray shown in *A*). The right main bronchus appears filled with granulation tissue projecting from the orifice of the right upper lobe bronchus. The carina and part of the left main bronchus are seen to the left of the drawing. The drawing *b* shows the appearance of the bronchus after most of the granulation tissue has been removed. A small amount still remains at the orifice of the right upper lobe bronchus (shortly before Fig. 2, *B*).

showed extrinsic compression of the bronchial wall by enlarged and presumably caseous lymph nodes. In one patient this alone was responsible for the obstruction, in the other three patients it was a contributory factor, and in one of these it was recognized to precede the endobronchial lesion by about a month (see Fig. 2, *A*). One patient gave a history suggestive of a foreign body in the bronchus and on roentgen examinations showed emphysema on the right side, apparently due to a check valve mechanism. At bronchoscopy a piece of firm caseous material the size of a large peanut was removed from the lumen of the right main bronchus. Histological examination revealed tuberculous tissue. This patient had, in addition, heaped up granulation tissue about what was believed to be the point of rupture in the bronchial wall through which the caseous material removed bronchoscopically had been extruded from an infected lymph node. The granulations were removed and the patient made a rapid recovery. She has been well for the past five years. In four of the twenty-nine patients bronchoscoped, the carina was moderately or markedly blunted but this was not considered evidence of obstruction. Eleven of the twenty-nine patients showed evidence of secondary pyogenic infection in the tracheobronchial tree. There were only three patients in the whole group who had a completely normal tracheobronchial tree from the bronchoscopic point of view. One of these had an active tuberculous pneumonia which had been treated for one month with streptomycin, the other two had had extensive tuberculous pneumonia twelve to fourteen years before bronchoscopy was done and both had ex-



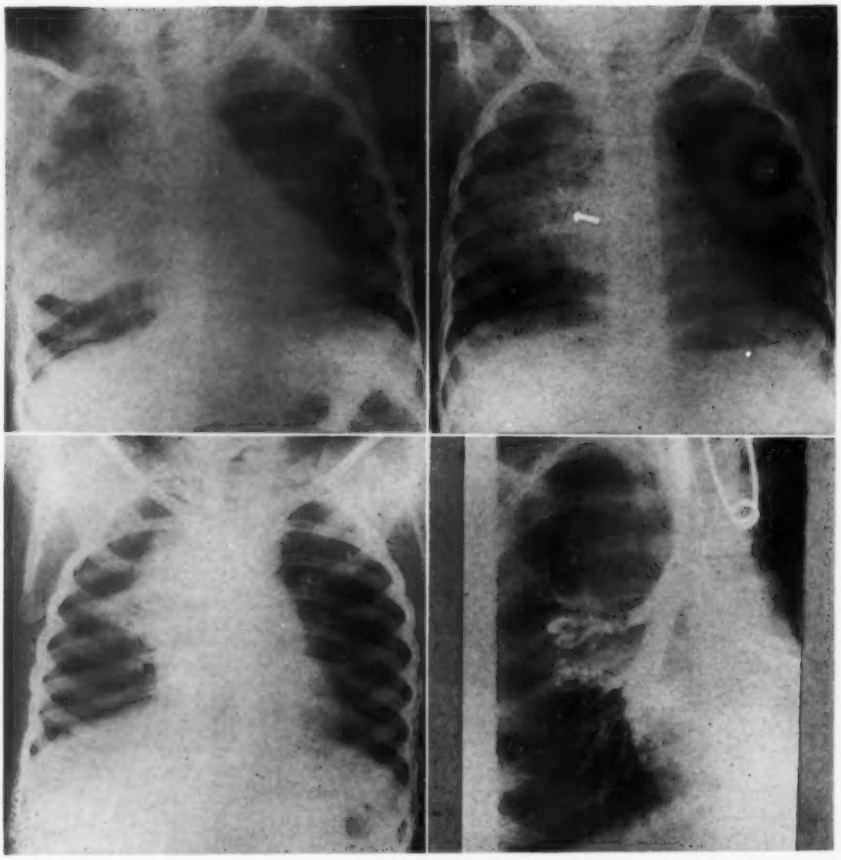
A. *B.*

Fig. 2.—P. W., a Negro female, aged 10 years.

A, The drawing *a* shows the left main bronchus as seen through a 6 mm. bronchoscope. The lateral wall of the bronchus is pushed in by pressure from without, reducing the size of the lumen by more than half. There was no evidence of endobronchial disease. A little mucoid discharge may be seen in the lumen. Drawing *b* shows the appearance one month later. During this interval the caseous node previously responsible for the bronchial compression has eroded through and discharged its contents into the bronchus. Granulation tissue has grown up around the point of rupture.

B, Roentgenographic appearance of the chest at the time when the first bronchoscopy was done. The tracheobronchial nodes on the left are enlarged and there is a parenchymal shadow representing at least in part atelectasis of the posterior segment of the left upper lobe. The roentgen appearance of the chest was unchanged at the time of the second bronchoscopic examination.

A. *B.*



C. *D.*

Fig. 3.—*A*, S. W., a Negro female, aged 1 year. Postprimary tuberculous pneumonia, bronchiectasis. This infant was admitted to the hospital ill with pneumonia. The tuberuclin test was positive. Roentgenogram of the chest shows a dense consolidation of the middle and part of the upper lobe of the right lung and enlargement of the paratracheal lymph nodes on the right.

B, S. W., aged 16 months. Roentgenogram made immediately following therapy with streptomycin of one-month duration. There has been some incomplete clearing of the pneumonic process but the paratracheal lymph nodes are still enormously enlarged. Note the narrowing of the right main bronchus below the level of the upper lobe orifice. This is assumed to be due to compression by enlarged bronchial lymph nodes.

(Fig. 3, *A* and *B*, courtesy Dr. H. Harrison, Baltimore City Hospitals.)

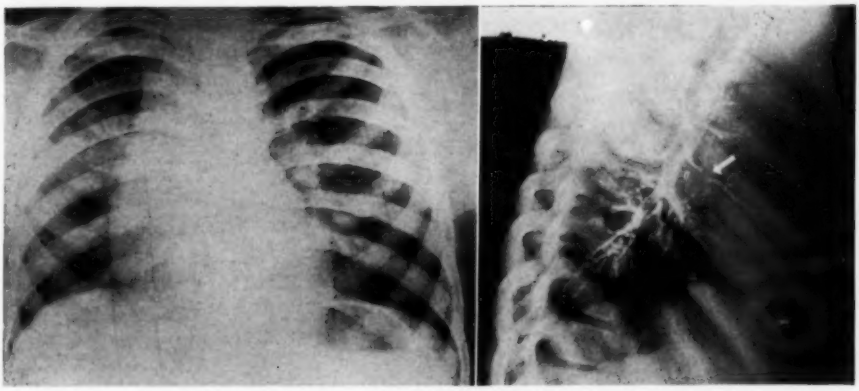
C, S. W., aged 21 months. There is still marked enlargement of the right paratracheal lymph nodes. The pneumonic consolidation appears to have undergone almost complete resolution. The child, who had been at home two months, began at this time to have fever, a productive cough, and to lose weight. She was admitted to the Harriet Lane Home. Bronchoscopic examination showed little beyond evidence of pyogenic infection of the right bronchial tree. Culture and guinea pig inoculation were negative for tubercle bacilli. Bronchographic study revealed a normal bronchial tree on the left (see *D*).

D, S. W., aged 23 months. "Spot" film of the bronchogram of the right side shows saccular bronchiectasis in the anterolateral (pectoral) division of the upper lobe, in the middle lobe (which is markedly reduced in volume), and in the dorsal division of the lower lobe. The secondary infection responsible for the present symptoms is being controlled with aureomycin so that the tuberculous process in the lymph nodes may subside. This child will undoubtedly require extensive pulmonary resection for permanent control of the bronchiectasis which has developed as the result of mechanical bronchial obstruction, plus secondary infection.

tensive saccular bronchiectasis at the time of bronchoscopy but were evidently free of secondary pyogenic infection.

2. Radiologic evidence of narrowing of the bronchial air shadow was present in seven children during the course of the acute tuberculous infection (see Fig. 3, *B*). Narrowing of the bronchial lumen was demonstrated by bronchography in two other patients (both with bronchiectasis) after the acute stage of the tuberculous infection had subsided (see Fig. 4, *B*).

3. The surgical pathological specimen of one patient (Fig. 5, *F*) showed narrowing of the bronchus to the posterior-basal segments of the left lower lobe by healed and scarred endobronchial disease.



A. *B.*

Fig. 4.—L. C., a Negro female, aged 8 years.

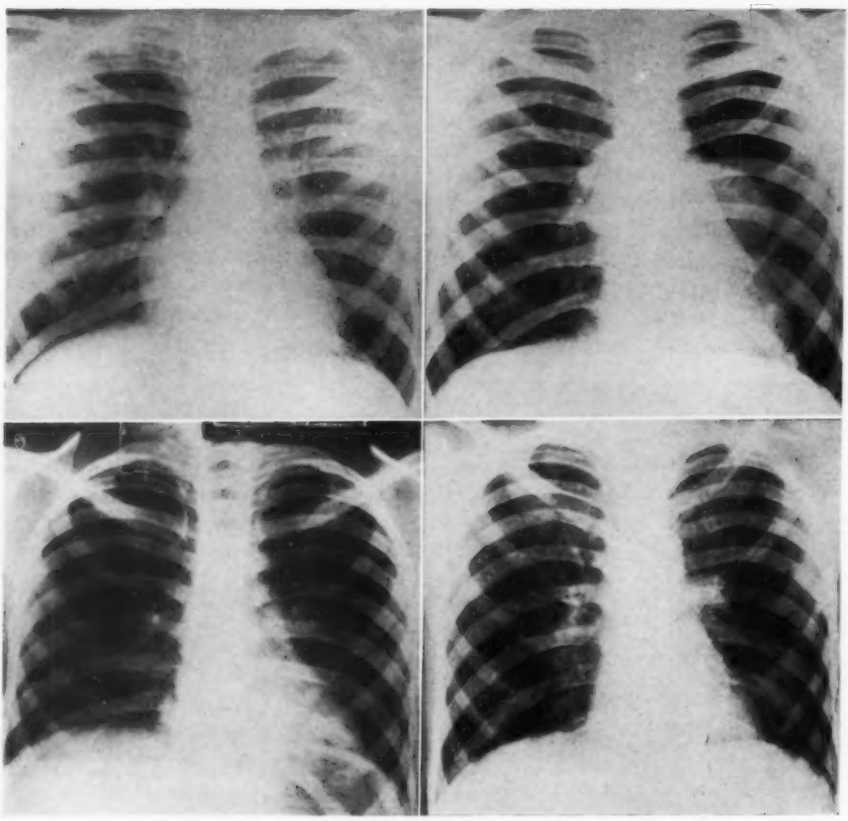
A, This youngster had been hospitalized for about six months because of a postprimary tuberculous pneumonia. Slight elevation of temperature and cough persisted. Roentgenogram shows an area of infiltration in the right mid-lung field. (Courtesy Henryton Sanatorium.)

B, Bronchoscopic examination showed inflammation and granulation tissue about the right middle lobe orifice. The bronchogram done at Henryton Sanatorium, of which the right lateral view is reproduced here, shows saccular bronchiectasis in the apical segment of the right lower lobe and marked constriction of the right middle lobe bronchus (indicated by the arrow), presumably the result of the endobronchial disease.

Two patients had radiologic evidence of actual enlargement of a pulmonary lobe. Bronchoscopic examination of one of these patients, an infant with enlargement of the right middle lobe, revealed apparently complete obstruction of the bronchus to the right middle lobe. We have observed one patient (not included in this study) who appeared during life to have a massive empyema on the left with shift of the mediastinum to the right. Autopsy demonstrated complete obstruction of the left main bronchus by tuberculous tissue with massive caseation of the greatly enlarged left lung.

Bronchial involvement was demonstrated in each of fifteen patients in whom bronchiectasis was found on reviewing 186 autopsy protocols of children dying of tuberculosis. In twelve of the fifteen patients there was evidence of rupture of an adjacent lymph node with discharge of caseous material into the bronchial lumen. In two

A. *B.*



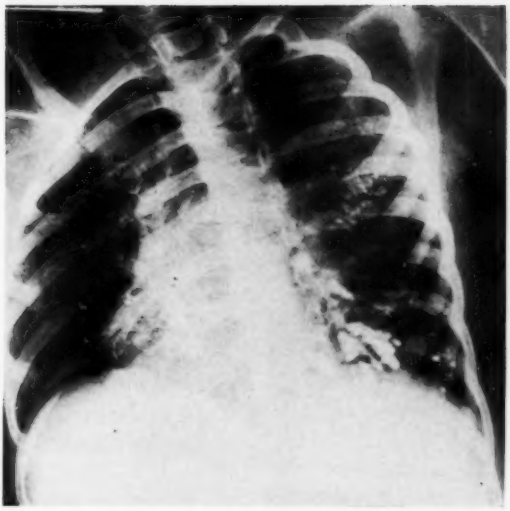
C. *D.*

Fig. 5.—*A*, A. J., a Negro female, aged 7 years. Bronchiectasis following bronchial occlusion and secondary infection in a patient with chronic hematogenous tuberculosis. This patient was found to react to 0.1 mg. O.T. on routine testing in March, 1944. Roentgenogram of the chest taken at that time was essentially normal. The patient was not seen again until September, 1945, when she had developed left axillary and cervical adenitis (proved by biopsy to be tuberculous).

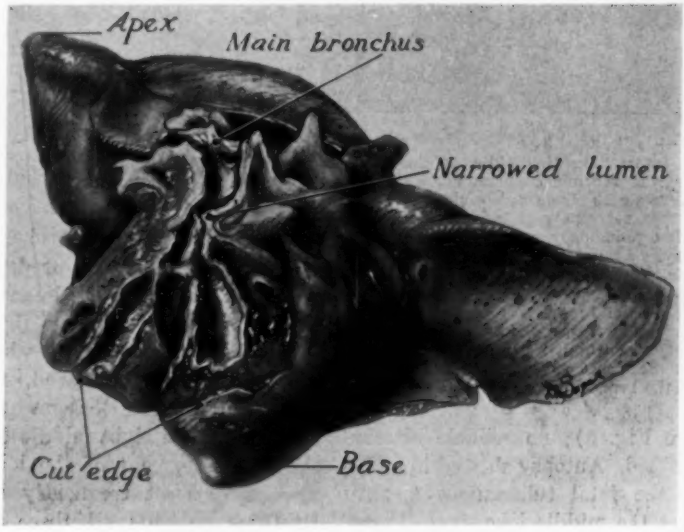
B, A. J., aged 9 years. Roentgenogram made in September, 1945, shows marked enlargement of the tracheobronchial lymph nodes on the left, with perhaps slight shift of the heart to the left. Had an overpenetrated or a lateral film been made, atelectasis in the left lower lobe could probably have been demonstrated. Cough was the only symptom of pulmonary disease.

C, A. J., aged 9½ years. Roentgenogram of the chest made in April, 1946, shows remarkable improvement although a faint outline of the mass of lymph nodes at the left lung root is still visible. Evacuation of the contents of a node into the bronchus is suspected. A large, firm mass, thought to be caseous mesenteric nodes, causing intermittent intestinal obstruction, was felt in the right lower quadrant.

D, A. J., aged 12 years. In September, 1949, the patient developed a transient attack of pneumonia accompanied by empyema, both of which responded rapidly to therapy with penicillin. No tubercle bacilli could be isolated on repeat of culture or guinea pig inoculation with the pleural fluid, gastric washings, or bronchoscopic material. Her chronic productive cough grew progressively worse, even though the roentgenogram of the chest cleared and appeared essentially normal. This plain roentgenogram was made in February, 1950.



E.



F.

Fig. 5.—*Cont'd*

E, A. J., aged 12 years. This oblique view of the bronchogram demonstrates moderately advanced bronchiectasis in the left lower lobe. The patient by this time was producing 50 to 100 c.c. of purulent sputum each day and was running a low-grade fever with afternoon spikes to 101° F. She was undernourished. The bronchiectasis was thought to be responsible for these symptoms. Medical therapy, to control infection (penicillin and aureomycin for four weeks and streptomycin for two weeks) and to reduce secretions (postural drainage and repeated bronchoscopic aspiration), was carried out for four weeks preoperatively.

F, A. J., aged 12 years. The left lower lobe was removed surgically in March, 1950. As may be seen from the drawing, thickening and stenosis of the posteromedial segmental bronchus near its origin was found with marked cylindrical bronchiectasis involving that whole segment (which has been laid open) below this point.

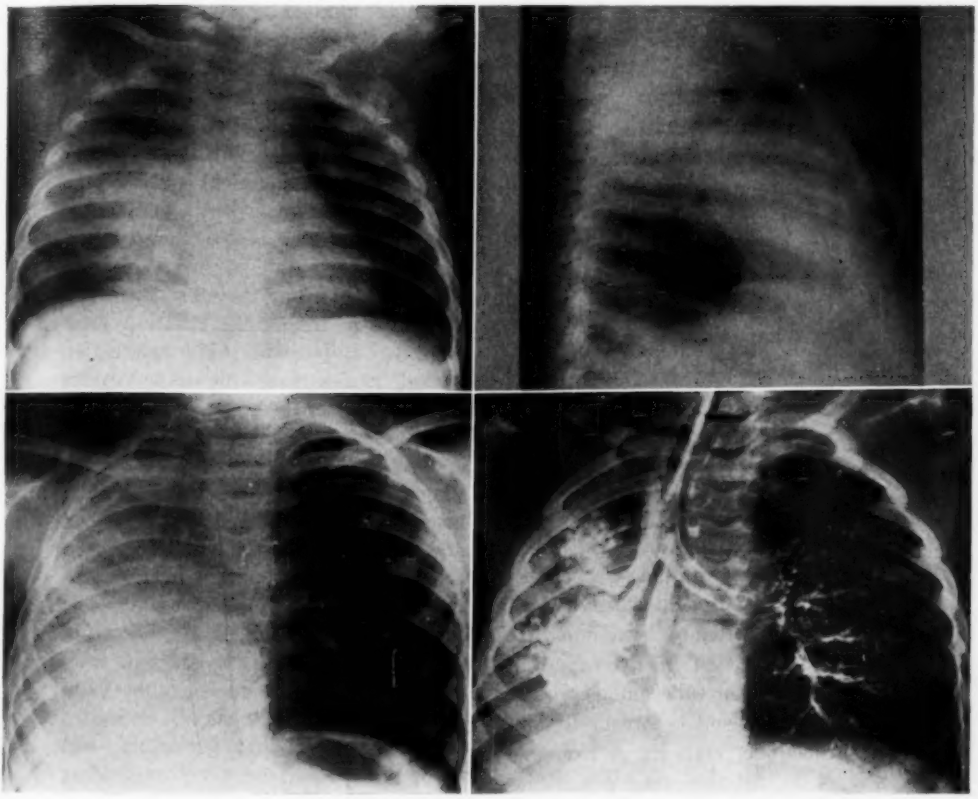
instances broncholiths were present in the lumen, and in one instance there was narrowing of the bronchus. This was an extremely interesting patient who died of tuberculous meningitis at the age of 3 years 9 months. The roentgenogram of the chest, made a few days before death, was essentially normal (see Fig. 6); no reliable history was obtained. Autopsy showed in addition to the fatal tuberculous meningitis that the middle lobe of the right lung was completely atelectatic and scarred with marked bronchial dilatation. The bronchus to the right middle lobe was markedly narrowed and thickened at its point of origin from the right main bronchus, and uniformly dilated distal to this point. There were small scarred and calcified hilar lymph nodes. The process found in this patient conforms exactly with Brock's description of the middle lobe syndrome.[2, 3] On reviewing the histories of these fifteen patients it was found that symptoms which could be attributed to secondary pyogenic infection were present in eleven.

Fig. 6.—A. R., aged 3 years 9 months. The point of interest in this child is that the roentgenogram reproduced here, made a few days before death from tuberculous meningitis, is apparently normal and gives no suggestion that pulmonary pathology was found at autopsy. At autopsy, in addition to the meningitis, the right middle lobe was found to be atelectatic, fibrotic, and bronchiectatic. The middle lobe bronchus was sharply narrowed and scarred, presumably the result of an old endobronchial tuberculosis. A partially calcified caseous lymph node lay adjacent to the bronchus.

II. *Bronchiectasis.*—Of the twenty-eight patients studied by means of bronchography there were eighteen whose tuberculosis was considered to have been inactive for a period of two years or longer. The total period of observation ranged from three and one-half to twenty-five years. In the remaining ten patients the tuberculous infection was still active and of no longer duration than two years; three of these had had tuberculosis for less than six months.

Bronchiectasis was demonstrated in twenty of the twenty-eight patients. This was saccular in nature in ten patients and tubular in ten. In this series all lobes are involved with almost equal frequency in contrast to Brock's series where involvement of the right middle lobe predominated. Although all lobes were involved with almost equal frequency there was marked selectivity as to which segment of a lobe was involved. The pectoral (anterolateral) segment of the upper lobe, the right middle lobe, and the apical segment of the lower lobe were those most frequently involved. In three patients all three of these areas on the right side were involved (see Fig. 3, *D*). In four patients all the lobes of one lung were involved, in two patients it was the right lung (Fig. 7), and in two the left. In the remaining thirteen patients involvement was limited to one lobe, often to one segment of a lobe, with the exception of two patients in whom both the

A. *B.*



C. *D.*

Fig. 7.—*A*, C. K., a Negro female, aged 1 year 5 months. The child had been exposed from birth to her tuberculous mother. The tuberculin test was positive to 0.1 mg. O.T. The chest film shows marked enlargement of the bronchial lymph nodes on the right and extensive involvement of the parenchyma. Stomach washings were positive for tubercle bacilli.

B, C. K., aged 1 year 5 months. The right lateral film demonstrates that the parenchymal lesion is at this time confined to the right middle lobe.

C, C. K., aged 6 years 9 months. The heart and mediastinum are completely shifted into the right hemithorax and the right diaphragm is elevated. The left lung appears normal except for compensatory emphysema. There has been no marked change in the roentgenological appearance of the chest since 3 years of age.

D, C. K., aged 6 years 9 months. Bronchography demonstrates a severe degree of saccular bronchiectasis throughout the right lung. (In two older patients with a similar condition the diseased lung was found to be essentially nonfunctioning by bronchospirometric studies.) This patient required pneumonectomy for control of the secondary pyogenic infection. Pathological examination of the removed lung showed only extensive scarring, bronchiectasis, and some calcification in the peribronchial lymph nodes. The tuberculous process had completely healed. A column of Lipiodol can be seen in the esophagus which also has been shifted into the right hemithorax.

right lower and middle lobes were involved.

Symptoms attributable to bronchiectasis were noted by nine of the twenty patients with this disease. These symptoms included frequent upper and lower respiratory tract infection, and in all but one patient at least one attack of acute bacterial pneumonia in the affected area. The onset of these symptoms varied between nine months (see Fig. 3) and five and one-half years (see Fig. 5), after tuberculosis was first diagnosed. It is noteworthy that the remaining eleven patients were free of symptoms even though in three instances the disease involved one entire lung. This is in keeping with the findings of Jones and associates[7] and Kent.[9]

Surgical extirpation has been deemed necessary in nine of the twenty patients with bronchiectasis. Seven patients have already been submitted to pulmonary resection, two others are waiting for the tuberculous process to become quiescent before undergoing this procedure.* In six of the seven patients treated (one total pneumonectomy right, one resection of the right upper lobe, one resection of the right middle and lower lobe, and three resections of the left lower lobe) the results have been excellent. The sixth, a 13-year-old girl, died immediately following pneumonectomy (left) from hemorrhage from the pulmonary artery. It may be stated that this is the first death in a series of approximately one hundred pulmonary resections in children done at The Johns Hopkins Hospital since January, 1944.

*These two patients have been successfully operated upon since this material first went to press.

DISCUSSION

Primary tuberculosis occurs when adequate numbers of viable tubercle bacilli gain entrance to the tissues of an individual lacking acquired resistance to tuberculous infection (through previous infection with the organism) and lacking hypersensitivity to tuberculoprotein. The clinical course of the disease may be divided into the incubation period which is considered to extend from the time of infection until the disease is first manifest by reversion of the tuberculin reaction from negative to positive. The incubation period varies from three to twelve weeks after exposure. The second period is that during which the disease is active and progression may take place; at this time symptoms of fever, cough, anorexia, etc., may be present and characteristic roentgenographic changes may be apparent. This stage may be of short duration or may last many months, even years. The third period is that of regression and healing. Healing takes place by means of fibrosis; calcium salts may be deposited in caseous areas. This period may last many months or years before healing is completed. The infection may be so mild that its entire course may pass unrecognized.

In its simplest terms the primary tuberculous process consists of (1) the primary focus, (2) an area of lymphangitis between the primary focus and the regional lymph nodes draining this area, and (3) lymphadenitis in the regional lymph nodes. The primary focus is usually situated peripherally adjacent to the pleura but may be anywhere in the lung. This lesion represents the portal of entry of the tubercle bacilli into the body. During the incubation period the bacilli grow

and multiply with relative rapidity in this area setting up a small focus of caseous pneumonia. Bacilli escape from the primary focus and are carried along the lymphatics (setting up a tuberculous lymphangitis) to the regional lymph nodes where a tuberculous lymphadenitis occurs. The lymph nodes involved in this process usually become markedly enlarged and caseous. Bacilli may be carried to other nodes in the lymphatic chain draining the area and they in turn may be involved. The incubation period comes to an end when tuberculin hypersensitivity becomes manifest; x-ray changes may become visible then or somewhat later. At about this time the effect of acquired resistance begins to be apparent. The multiplication of bacilli, which has been rapid, begins to slow down and the process eventually starts to heal if no complications occur. The complications which may alter the course of events result from (1) the escape of bacilli into the blood stream allowing hematogenous dissemination to other parts of the body, (2) compression of adjacent structures by enlarged tuberculous lymph nodes, and (3) direct extension of the tuberculous process may occur if the infected lymph node ruptures through its capsule. This is of particular consequence where the lymph nodes encroach upon relatively rigid structures such as bronchi which cannot easily be displaced; the pressure exerted results then in softening of the bronchial wall, perhaps as the result of ischemic necrosis, perhaps as the result of actual tuberculous involvement. As the process in the node continues its capsule thins out and eventually the integrity of the capsule is lost; the bronchial wall may then become involved in the tuberculous process. Eventually the infected node may erode through the bronchial wall and its caseous contents may be discharged into the lumen of the bronchus. Tuberculous granulation tissue grows up around the point of rupture further reducing the size of the lumen or even completely occluding it. The occlusion of the bronchus either by pressure from without or by the presence of endobronchial lesions results in atelectasis in the segment supplied by that bronchus.

As may be seen from Fig. 8, the lymph nodes most likely to be involved first in the process are the bronchial (pulmonary) nodes lying adjacent to the bronchi to the lobar segments; the next most likely are the hilar group of nodes lying across the main bronchi, then the tracheobronchial, and last, the tracheal nodes. The lymph nodes at the bifurcation are involved with considerable frequency as drainage into them can occur from either side. The anatomical distribution of the lymph nodes seems to us to account for the high frequency of segmental involvement by the obstructive and subsequently bronchiectatic process. The relatively large number of nodes lying about the bronchus to the pectoral (anterolateral) division of the upper lobes, the apical division of the lower lobes, and the right middle lobe render these particular segments more vulnerable than others.

When the infected lymph node ruptures through into bronchi, caseous material is spilled into the bronchus and aspirated distally. This material may act as a mechanical block causing obstruction. If it contains viable tubercle bacilli it may cause a tuberculous pneumonia in the area of lung

supplied by the involved bronchus; if there are few or no viable bacilli it may give rise to a so-called benign "epituberculosis," really an acute hypersensitivity reaction to the tuberculoprotein (from dead tubercle bacilli, Oppenheimer[13]) in the caseous material spilled. This cannot be distinguished radiologically from a true tuberculous pneumonia. The diagnosis is made largely on the basis of a benign course of relatively short duration. Neither "epituberculosis" nor a true tuberculous pneumonia resulting from aspiration of caseous material can readily be distinguished radiologically from atelectasis resulting from simple bronchial occlusion.

Bronchial obstruction and bronchiectasis complicating primary tuberculosis have been encountered in young children and in adults. The youngest patient in whom bronchiectasis complicating primary tuberculosis was found by bronchography was 20 months of age (see Fig. 3). We have seen this process develop in a Negro woman (not included in this study) who first presented evidence of primary infection with large lymph nodes at 40 years of age, and who, at 48 years, has bronchiectasis in the involved area. The process may be of fairly frequent occurrence in Negro adults where marked enlargement of the lymph nodes not infrequently complicates the primary infection. This is very seldom the case in white adults. Eight of the fifteen children found to have bronchiectasis at autopsy were less than 2 years old. The high incidence in this group is undoubtedly due to the fact that tuberculosis is a serious disease in children under 2 years

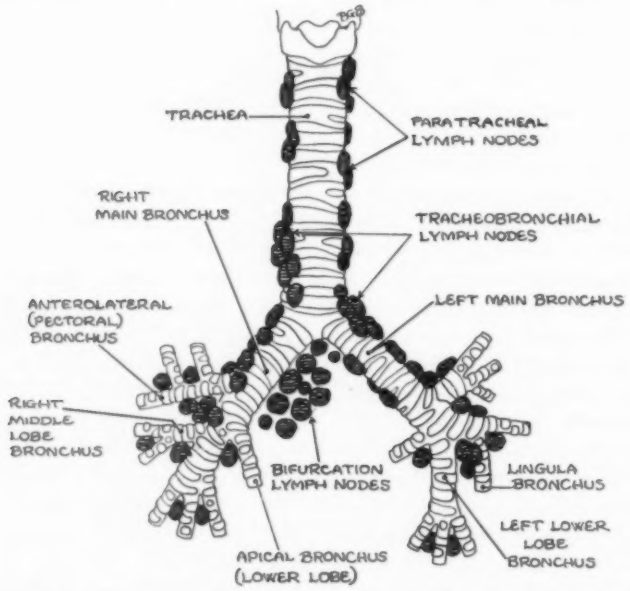


Fig. 8.—Distribution of the tracheobronchial lymph nodes. (Semidiagrammatic drawing after W. Snow Miller: *The Lung*, Springfield, Ill., 1937, Charles C Thomas.)

of age whereas the mortality rate is very low in children between 3 and 10 years of age.

The finding of bronchiectasis, as described in the autopsy protocols, of only fifteen of 186 children dying of tuberculosis is worthy of comment. Only the more gross degrees of bronchial dilatation are noted in the pathological specimens unless this condition is specifically sought. The above findings were discussed with Dr. Arnold Rich (Professor of Pathology, The Johns Hopkins University School of Medicine) who felt that this small percentage did not represent the true prevalence of this complication and that had the condition been specifically looked for more cases would have been found.

The high incidence of saccular (cystic) bronchiectasis in this series seems worthy of comment. Ten (50 per cent) of twenty patients had this type of disease. Field[5] reported that 20 per cent of 160 patients (in only four of whom was it supposed that tuberculosis was an etiological factor) had this type of disease. In 85 per cent of her cases the left lower lobe was involved and in 65 per cent, the lingula, in contrast to our small series of cases where the distribution was quite general.

The realization that bronchiectasis is of frequent occurrence in adult tuberculosis is not new. Dormer,[4] Rilance and Gerstl,[14] Jones and associates,[8] and others have published extensive reports as to its characteristics and occurrence. The bronchiectatic lesions in reinfection tuberculosis apparently represent the actual site of tuberculous disease in contrast to the bronchiectatic lesions following primary tuberculous infection. In children the very nature of the pathological process in primary tuberculosis lends itself to the production of bronchial obstruction (in any one or a combination of the following ways):

1. Extrinsic pressure upon the bronchial wall by enlarged lymph nodes (illustrated by Figs. 2 and 3).

2. Acute endobronchial disease resulting from rupture of caseous lymph nodes through the bronchial wall, with heaping up of granulation tissue, is the usual finding in endobronchial disease in children (illustrated by Fig. 2).

3. Acute endobronchial disease with edematous, inflamed, and ulcerated mucous membrane as seen in the adult type of disease is encountered but rarely in children. We have seen but one child, a 5-month-old infant, with a postprimary tuberculous pneumonia with this type of endobronchial disease.

4. Actual presence of caseous material in the bronchus.

5. Healing of a bronchial perforation with scarring and stricture formation (illustrated by Fig. 5).

The development of bronchiectasis appears to depend upon a combination of mechanical obstruction and secondary pyogenic infection. The combination of these two factors with the damage to natural defenses resulting from poor drainage and destroyed bronchial mucosa allows permanent damage of bronchi and lung tissue to develop.

Bronchoscopy when skillfully done with instruments of suitable size is perfectly safe even in newborn infants. Approximately 700 bronchoscopic examinations have been done on children in The Johns Hopkins Hospital since January, 1944, without serious complications (except in one instance, a baby 2 weeks old with a serious and

complicated malformation of the trachea elucidated only at autopsy). Lowys, Tison, and Metivier[10] report that the bronchoscopic examination of 129 children, all with tuberculosis, was not attended by complication. They report findings considered abnormal in 100 of these 129 patients; in general, these findings were nonspecific compression, secondary infection, edema, hypersecretion, etc. In five children a lymph node had ruptured into a bronchus; in six, granulations were observed; and in six, ulcerations of the bronchial mucous membrane were seen. These patients were presumably examined during the acute phases of their tuberculosis and bronchiectasis was found in only six of the children.

Some idea of the prevalence of bronchiectasis as a complication of primary tuberculosis associated with segmental pulmonary atelectasis can be obtained from the work of Roberts and Blair.[15] Of 400 children with primary pulmonary tuberculosis followed by them, seventy-seven (19 per cent) showed collapse of a pulmonary segment or lobe, or of an entire lung. Of the seventy-seven children with collapse, forty-six (60 per cent) developed evidence of bronchiectasis. In twelve of the children the bronchiectasis was obvious on routine roentgenograms. In the remaining thirty-four it was found on bronchography. The remaining thirty-one children who had evidence of atelectasis were followed up to a period of seven years after the development of the collapse and none developed evidence of bronchiectasis. Veeneklaas[16] has also reported a high incidence of residual pulmonary and bronchial damage following primary tuberculosis.

CONCLUSION

The fact that bronchiectasis may complicate primary pulmonary tuberculosis seems well established. Etiological factors of importance are prolonged bronchial obstruction and the secondary infection attendant upon poor bronchial drainage. Since obstruction frequently results from the presence of endobronchial granulation tissue and occasionally from the presence of caseous material lying free in the bronchus, early bronchoscopy in patients with evidence of obstruction is indicated for the relief of the obstruction by surgical removal of granulation tissue and/or aspiration of foreign material from the bronchus.

SUMMARY

1. Thirty-five patients with evidence of bronchial obstruction secondary to primary tuberculous infection were studied.

2. Twenty-nine patients were bronchoscoped; of these

a. Eleven had evidence of partial or complete bronchial occlusion which in one instance appeared due to extrinsic pressure alone and in ten instances was due to endobronchial disease or a combination of endobronchial disease and extrinsic pressure,

b. Five (all with active tuberculous lesions of only a few months' duration) had evidence of acute infection nonspecific in type,

c. Eleven had evidence of chronic secondary pyogenic infection,

d. Three had no evidence of endobronchial disease.

3. Twenty-eight patients had bronchographic studies done, and of these, twenty were found to have bronchiectasis. This was of the saccular (cystic) variety in ten patients and tubu-

lar in ten. The bronchiectatic changes were found equally distributed between all the pulmonary lobes but showed preponderance in the anterolateral (pectoral) segment of the upper lobes, the apical segment of the lower lobes, and the right middle lobe. This is believed to be related to the distribution of the lymphatic nodes in these areas.

4. The autopsy protocols of 186 children dying of tuberculosis were reviewed. Fifteen children were found to have bronchiectasis as a complication of primary tuberculous infection.

5. Bronchoscopic examination is important when there is clinical evidence of bronchial obstruction or roentgenological evidence of pulmonary involvement in a tuberculous process of greater extent than a simple primary focus as bronchoscopic relief of the obstruction may be possible.

6. Abnormal physical signs and symptoms, and roentgen-ray findings occurring after the primary tuberculous infection has had reasonable time to subside may result from superimposed bronchiectasis. This can only be satisfactorily investigated by bronchography. Surgical therapy may be necessary in some patients to control symptoms of secondary pyogenic infection.

REFERENCES

1. Brock, R. C.: Lecture before the staff of The Johns Hopkins Hospital, 1949.
2. Brock, R. C.: Post-tuberculous Bronchostenosis in Bronchiectasis of the Middle Lobe, Thorax **5**: 5, 1950.
3. Brock, R. C., Cann, R. J., and Dickinson, J. R.: Tuberculous Mediastinal Lymphadenitis in Childhood; Secondary Effects on Lungs, Guy's Hosp. Rep. **87**: 295, 1937.
4. Dormer, B. A., Friedlander, J., and Wiles, F. J.: Bronchography in Pulmonary Tuberculosis:
   I. Normal or Questionable Roentgenographic Findings in Lungs and Positive Sputum, Am. Rev. Tuberc. **50**: 283, 1944.
   II. Radiographic Black-out: Evaluation of Underlying Lesions, Am. Rev. Tuberc. **50**: 287, 1944.
   III. Chronic Fibroid Phthisis: Chronic Productive Tuberculosis, Am. Rev. Tuberc. **51**: 62, 1945.
   IV. A Geographical Adventure, Part 1, Am. Rev. Tuberc. **51**: 455, 1945.
   V. A Geographical Adventure, Part 2, Am. Rev. Tuberc. **51**: 519, 1945.
5. Field, C. E.: Bronchiectasis in Childhood:
   I. Clinical Survey of 160 Cases, Pediatrics **4**: 21, 1949.
   II. Aetiology and Pathogenesis, Including a Survey of 272 Cases of Doubtful Irreversible Bronchiectasis, Pediatrics **4**: 231, 1949.
   III. Prophylaxis, Treatment, and Progress With Follow-up Study of 202 Cases of Established Bronchiectasis, Pediatrics **4**: 355, 1949.
6. Hughes, J. G., and Simpson, W. S.: Bronchiectasis Following Atelectasis in Tuberculosis of Infancy; Role Played by Enlarged Glands and Granulation Tissue, J. PEDIAT. **17**: 197, 1940.
7. Jones, E. M., Peck, W. M., and Willis, H. S.: Bronchiectasis Following Primary Tuberculosis, Am. J. Dis. Child. **72**: 296, 1946.
8. Jones, E. M., Peck, W. M., and Willis, H. S.: Relationships Between Tuberculosis and Bronchiectasis, Am. Rev. Tuberc. **61**: 387, 1950.
9. Kent, E. M.: Bronchial Obstruction and Pulmonary Atelectasis, as Seen in Childhood Tuberculosis With Secondary Bronchiectasis as Sequela, Am. Rev. Tuberc. **46**: 524, 1942.
10. Lowys, P., Tison, F., and Metivier, O.: La bronchoscopie chez l'enfant soigné en sanatorium, Poumon **5**: 281, 1949.
11. Meneghello, J., and Smith, C. A.: Obstruction Emphysema and Atelectasis in Tuberculosis of Infants and Children, J. PEDIAT. **22**: 265, 1943.
12. Mitchell, E. B., and Thornton, T. F., Jr.: Lower Lobe Bronchiectasis Associated With Tuberculosis, Am. Rev. Tuberc. **49**: 38, 1944.
13. Oppenheimer, E. H.: Experimental Studies on the Pathogenesis of Epituberculosis, Bull. Johns Hopkins Hosp. **52**: 247, 1935.
14. Rilance, A. B., and Gerstl, B.: Bronchiectasis Secondary to Pulmonary Tuberculosis, Am. Rev. Tuberc. **48**: 8, 1943.
15. Roberts, J. G., and Blair, L. G.: Bronchiectasis in Primary Tuberculous Lesions Associated With Segmental Collapse, Lancet **258**: 386, 1950.
16. Veeneklaas, G. M. H.: Cause and Sequela of Intrapulmonary Shadows in Primary Tuberculosis, Am. J. Dis. Child. **83**: 271, 1952.

FURTHER STUDIES OF THE EFFECTS OF CITRATE FEEDING ON THE CALCIUM, PHOSPHORUS, AND CITRATE METABOLISM OF RACHITIC INFANTS

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WITH THE TECHNICAL ASSISTANCE OF FLO MOHR, A.B., AND EVELYN FLEISHMAN, B.SC.

THE discovery that the bone lesions of vitamin D deficiency can be healed by administration of citrate[1, 2] resulted from attempts to define the biochemical basis of vitamin D activity. Our interest in this problem stems again from efforts to learn more of the mechanisms whereby vitamin D regulates the concentrations of calcium and phosphorus in the body fluids and influences the deposition of these ions in bone. Hamilton and Dewar[1] thought that increased utilization of calcium and phosphorus would be promoted by the administration of organic acids and their salts in proportions which would reduce the pH of the intestinal contents and yet tend to produce a metabolic alkalosis. They found that mixtures of tartaric or citric acid and their sodium salts were effective in the prevention of rickets in rats. Shohl[2] confirmed the antirachitic effect of mixtures of citric acid and sodium citrate but found that a number of other organic acids were ineffective when given in comparable dosage. He concluded that only those organic acids which formed undissociated complexes with calcium were effective antirachitic agents. Citrate was more effective than tartrate in the prevention and healing of rickets and also more efficient in the removal of calcium ions from solution. Shohl and Butler,[3] Eliot and Park,[4] and Rominger[5] fed mixtures of citric acid and sodium citrate to infants with rickets due to vitamin D deficiency and found healing of the rickets occurred without addition of vitamin D to the diet. Rominger and his co-workers[6, 7] suggested, among other theories, that citrate functions by the formation of a soluble calcium citrate complex in the intestinal tract which promotes the absorption of calcium and increases the availability of diffusible calcium for deposition in bone. They further postulated that the increased absorption of calcium inhibits the hyperfunction of the parathyroids which supposedly occurs in rickets as a reaction to calcium deficiency. This explanation is attractive by virtue of its simplicity but fails to account for some of the phenomena observed when citrates are given to rachitic infants. Two rachitic infants treated with citrate mixtures by Shohl and Butler[3] showed a considerable decrease in the concentrations of serum calcium at the time that x-ray evidences of healing of the rickets were noted. In these infants calcification of rachitic cartilage progressed despite Ca × P products below 30 which are ordinarily considered incompatible with deposition of bone salts. This does not support the notion that the chief function of citrate is to increase the availability

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of calcium and phosphorus to the body by increasing the solubility of calcium in the intestinal contents.

The phenomenon of calcification of bone matrix despite persistently low concentrations of calcium and phosphorus in extracellular fluid seemed of sufficient theoretical interest to warrant further studies of the effect of citrates in rickets. We have treated three rachitic infants with citrate mixtures similar to those of Shohl and Butler.[3] These infants were kept on a diet low in vitamin D, consisting of whole boiled cow's milk, cereal, vegetables, and ascorbic acid. The diet was kept constant throughout the period of study. Samples of blood were obtained at intervals for determination of serum calcium, phosphorus, citrate and alkaline phosphatase. Urine was collected quantitatively over twenty-four-hour periods and analyzed for citrate, phosphorus, and calcium. The urine was preserved by the addition of 25 c.c. of 10 per cent acetic acid to the bottle. X-rays of the long bones were taken at approximately weekly intervals. The methods used for analysis of blood and urine were as follows: calcium, Kramer and Tisdall[8]; phosphorus, Fiske and Subbarow[9]; citrate, Natelson, Pineus, and Lugovoy[10]; alkaline phosphatase, Bodansky.[11]

RESULTS

Case 1.—Patient R. R. was a 17-month-old boy admitted to the Harriet Lane Home because of severe rachitic deformities. He had been breast fed and then started on cow's milk and solid foods but vitamin D-containing preparations were given only sporadically. The x-rays of the bones showed florid rickets. The concentration of calcium in the serum was 9.0 mg. per 100 c.c. and that of phosphorus 3.3 mg. per 100 c.c. The level of alkaline phosphatase was 38 Bodansky units. The results of the analyses of serum and twenty-four-hour specimens of urine obtained after he was placed on the experimental regimen are diagrammed in Fig. 1. After nine days of preliminary observation citrate was added to the diet. Fifty cubic centimeters of a molar solution of citrate containing citric acid and trisodium citrate in equimolar proportions were given daily. The day following the institution of citrate treatment the concentration of calcium in serum dropped to 6.6 mg. per 100 c.c. and only slowly rose to levels between 8 and 9 mg. per 100 c.c. Before treatment with citrate the serum citrate values averaged 2.1 mg. per 100 c.c. which is at the lower limits of the normal range. During the period of citrate therapy the serum citrate level varied between 1.7 and 2.6 mg. per 100 c.c., averaging 2.1 mg. per 100 c.c. The excretion of citrate in the urine did not increase immediately with the beginning of citrate treatment but after about ten days of treatment an increased excretion of citrate in the urine occurred. The difference between the average value of 119 mg. per day before treatment and the average excretion of 203 mg. per day during the period of maximum urinary excretion of citrate is minute, however, in comparison with the added intake of citrate which was 50 mM. per day equivalent to 9.6 Gm. of citric acid per day. The urinary excretion of phosphate showed no real change following citrate administration and the excretion of calcium in the urine remained low throughout the entire period, never rising above 15 mg. per day. Despite the depressed levels of serum calcium and phosphorus, x-ray evidences of healing were seen on the twenty-fifth day of the citrate period (day 34 of chart). On the twenty-seventh day of citrate treatment 600,000 units of vitamin D were given by intramuscular injection with continuation of the same daily dose of citrate. With this dose of vitamin D there was little change in the concentrations of calcium, phosphorus, or citrate in the

serum although continued calcification of rachitic cartilage was seen by x-ray. A second injection of 600,000 units of vitamin D was given fourteen days later and following this the concentration of phosphorus in serum rose progressively, reaching values above 5 mg. per 100 c.c.; the serum calcium level rose to 10 mg. per 100 c.c.; and the concentration of citrate increased to 3 mg. per 100 c.c. or more. The levels of serum alkaline phosphatase which were persistently elevated between 40 and 60 units during the period of citrate treatment increased abruptly following each injection of vitamin D but finally dropped as healing progressed. At the termination of the study the x-rays of the bones showed satisfactory healing of the rachitic process.

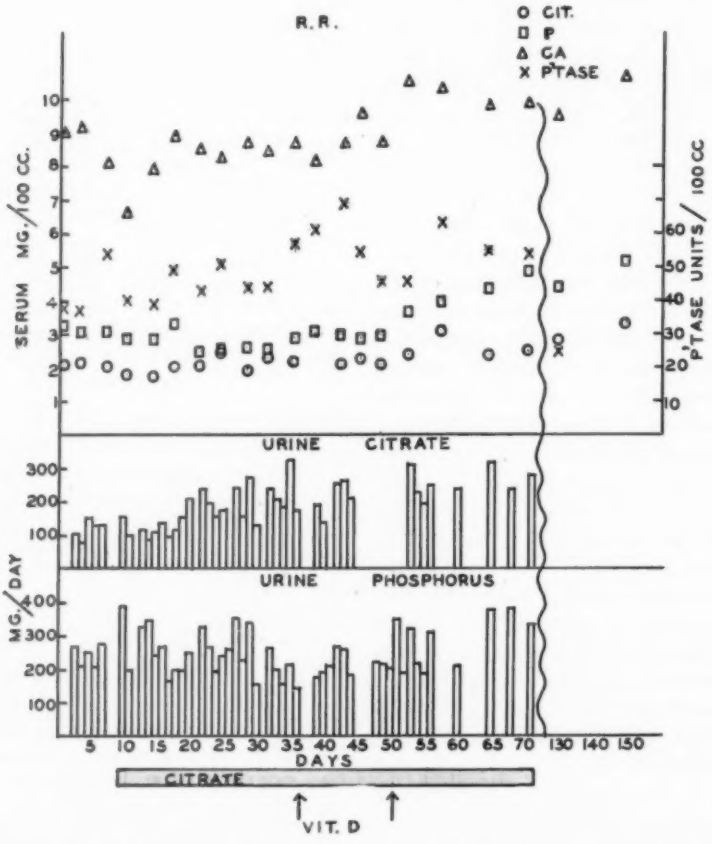

Fig. 1.—Patient R. R. Effects of feeding citrate without vitamin D to rachitic infant compared with effects of vitamin D administration. The columns represent twenty-four-hour excretions of phosphorus and of citrate in the urine. The serum values are represented by the following symbols: calcium △, phosphorus □, citrate ○, and alkaline phosphatase ×. Fifty cubic centimeters of molar citrate solution were given daily during the period shown by the shaded bar. The arrows indicate injections of vitamin D, each dose being 600,000 units.

Case 2.—The second case studied was E. B., a 19-month-old boy also admitted to the Harriet Lane Home because of marked bony deformities and

characteristic x-ray findings of florid rickets. This boy had been breast fed up to the time of admission with the addition of some solid foods to his diet. No vitamin D supplement had been given.

citrate was in the normal range averaging 2.6 mg. per 100 c.c. contrary to the more usual finding of a reduced level of serum citrate in vitamin D deficiency states.[12] The levels of serum alkaline phosphatase were exceedingly

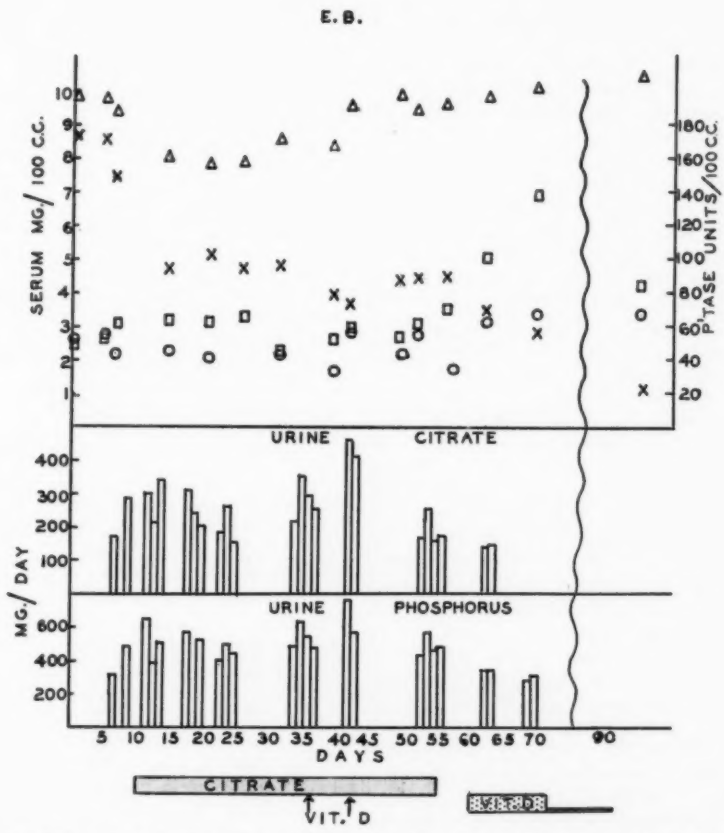

Fig. 2.—Patient E. B. Effects of feeding citrate without vitamin D to a rachitic infant compared with subsequent effects of vitamin D. The columns represent twenty-four-hour excretions of phosphorus and of citrate in the urine. The serum values are represented by the following symbols: calcium △, phosphorus □, citrate ○, and alkaline phosphatase ×. Sixty cubic centimeters of molar citrate solution were given daily during the period shown by the shaded bar. The arrows indicate injections of vitamin D, each dose being 600,000 units. The period of oral administration of vitamin D is shown by the stippled bar.

During the preliminary period of observation on the standard diet the concentration of calcium in serum averaged 9.0 mg. per 100 c.c. and that of phosphorus 2.7 mg. per 100 c.c. (Fig. 2). The concentration of serum

high with a peak value of 180 Bodansky units. On the tenth day, citrate therapy was begun and 60 mM. of citrate were given daily in divided doses. The concentration of serum calcium dropped rapidly to 7.8 mg. per 100

c.c. and did not rise above 8.6 mg. per 100 c.c. during the period of treatment. The levels of serum phosphorus showed little change remaining at about 3 mg. per 100 c.c. and the concentration of serum citrate decreased slightly. In this patient the urinary excretion of citrate did not increase during the period of citrate therapy but showed a temporary rise when vitamin D was also given. The loss of phosphate in the urine was not altered by the citrate treatment and the urinary excretion of calcium which is not shown in the figure was extremely low throughout. X-ray evidences of calcification of rachitic cartilage were seen on the twelfth day of treatment (day 22 on chart) despite, as in case R. R., persistently low levels of calcium and phosphorus in the serum. On the twenty-sixth and thirty-second days of treatment injections of 600,000 units each of vitamin D were given which were without effect upon the serum phosphorus levels although the concentration of calcium in serum rose above 9 mg. per 100 c.c. The administration of citrate was discontinued after forty-five days. Two days later the concentration of citrate in the serum was reduced to 1.7 mg. per 100 c.c. At this time x-rays of the long bones showed considerable but incomplete healing. Because of the failure to achieve normal levels of serum phosphorus after injection of a total of 1,200,000 units of vitamin D, further vitamin D was given orally in a dosage of 50,000 units per day for twelve days following which the dose was reduced to 5,000 units per day. With this treatment the concentration of serum phosphorus rose rapidly to a maximum of 6.9 mg. per 100 c.c. and the level of serum citrate increased to 3.3 mg. per 100 c.c. Serial x-rays showed progressive healing of the bone lesions. During the period of citrate treatment the alkaline phosphatase activity in the serum dropped from the initial extraordinarily high levels and continued to decrease during vitamin D therapy. Although this patient required an unusually large amount of vitamin D the eventual response was similar to that seen in the ordinary case of vitamin D deficiency rickets given more usual doses of vitamin D.

In an effort to learn whether the antirachitic activity of citrate was associated with some humoral factor which influenced the calcification of rachitic cartilage, in vitro studies of calcification of rachitic rat cartilage in this patient's serum were made. Slices of the proximal portion of the tibias of rachitic rats were made under aseptic conditions and incubated for eighteen hours at 37° C. in about 5 c.c. of sterile serum. Following incubation the tibial slices were fixed in neutral formalin, washed, and stained for calcium salts by the silver nitrate method. Control unincubated slices of tibias were similarly stained and in vitro calcification of the rachitic cartilage determined by comparison of the control and incubated specimens. No in vitro calcification could be demonstrated in the specimens incubated in serum samples taken on the sixteenth and twenty-sixth days of citrate therapy. The Ca × P products in the serum samples before incubation were 26 and 20, respectively, on these days. In vitro calcification of rachitic rat cartilage was found when the rat tibia was incubated in serum obtained from the patient following intensive vitamin D therapy when the Ca × P product in the serum sample was 70. The occurrence of in vitro calcification seems to be related only to the concentrations of calcium and phosphorus in the medium whereas x-ray evidence of in vivo calcification was seen despite concentrations of these ions in body fluids which were too low to permit calcification under in vitro conditions.

CASE 3.—O. P. presented a different aspect of vitamin D deficiency. This infant was prematurely born at another hospital from which he was discharged at 2 weeks of age. He was poorly cared for at home but, according to the history, was given feedings of evaporated milk mixtures. The mother's story was unreliable and the prescribed supplements of vitamin D

were probably not given. He was admitted to the Baltimore City Hospitals at 2 months of age because of the sudden onset of convulsive seizures on the day of admission. At this time he weighed 3,570 grams and on examination he was an undernourished infant having frequent short generalized convulsions. The Chvostek and peroneal signs were positive. The concentration of calcium in the serum taken immediately after admission was found to be 4.4 mg. per 100 c.c. In another sample of serum taken several hours later the serum calcium level was 5.7 mg. per 100 c.c., and that of phosphorus 5.1 mg. per 100 c.c. The concentration of nonprotein nitrogen was 27 mg. per 100 c.c. and the level of serum protein 5.6 Gm. per 100 c.c. The serum alkaline phosphatase activity was increased to 58 Bodansky units and the concentration of serum citrate was 1.7 mg. per 100 c.c. The x-rays of the long bones showed laminated periosteal lines but there were no characteristic rachitic changes at the metaphyseal ends. The diagnosis of rickets was made on the basis of hypocalcemia without elevation of the serum phosphorus values, the high levels of serum alkaline phosphatase, and the x-ray evidence of subperiosteal proliferation of osteoid. Subperiosteal encasements of this type are seen in the bones of premature infants and their significance is not always clear but in some premature infants they have been thought to be early manifestations of rickets.[13] Soon after admission the in-

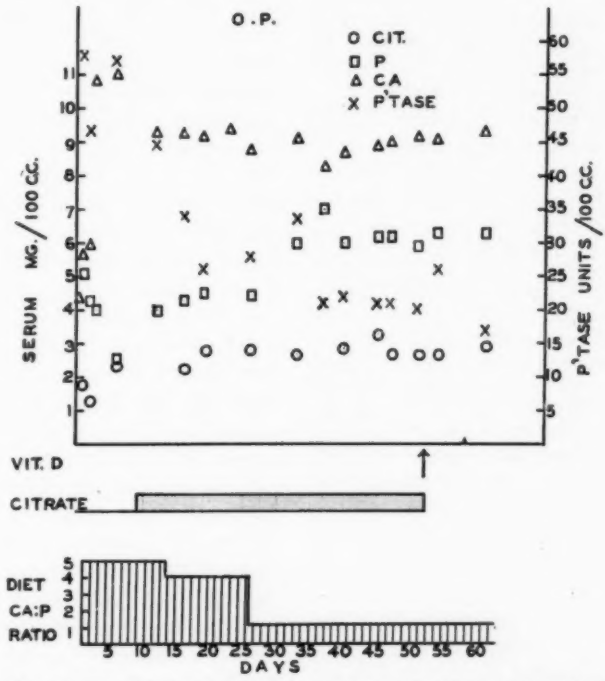

Fig. 3.—Patient O. P. Effects of high calcium low phosphorus diet and citrate feeding in a 2-month-old infant with rickets and tetany. The serum values are indicated by the following symbols: calcium △, phosphorus □, citrate ○, and alkaline phosphatase ×. The ratio of calcium to phosphorus in the diet is shown at the bottom of the figure. The period of citrate feeding is shown by the shaded bar. The arrow indicates the intramuscular injection of 600,000 units of vitamin D.

fant was given calcium gluconate intravenously and the following day the oral calcium intake was increased by the addition of 6 Gm. of calcium lactate, equivalent to 780 mg. of calcium, to a high carbohydrate feeding mixture prepared from a low fat milk, Alacta with added carbohydrate. The total calcium intake was 1 Gm. per day with a Ca:P ration of 5:1. No vitamin D was given. On the ninth day molar citrate mixture was added to the feeding, 30 c.c. per day in divided amounts. The results of serum analyses are summarized in Fig. 3.

Following addition of extra calcium to the diet the serum calcium level rose rapidly to 11 mg. per 100 c.c. and the concentration of serum phosphorus dropped progressively to 2.5 mg. per 100 c.c. When citrate was added to the high calcium feedings the serum calcium values dropped to 9.0 mg. per 100 c.c. but did not decrease to the low levels seen in the two preceding patients. The concentration of serum phosphorus rose again to values of 4.0 to 4.5 mg. per 100 c.c. After seventeen days of citrate therapy the extra calcium was removed from the diet and the citrate continued. The serum phosphorus levels rose further to between 6 and 7 mg. per 100 c.c. with a temporary drop in the concentration of serum calcium below 9 mg. per 100 c.c. The serum alkaline phosphatase activity decreased progressively. The serum citrate levels were low on admission averaging 1.5 mg. per 100 c.c. and rose progressively during the period of citrate treatment to about 3 mg. per 100 c.c. X-rays of the long bones showed calcification of the subperiosteal osteoid and good bone growth with normal metaphyseal and epiphyseal calcification. At the end of forty-three days of citrate therapy the citrate was discontinued and the infant given 600,000 units of vitamin D intramuscularly. There was no immediate change in the concentrations of calcium and phosphorus and the serum alkaline phosphatase activity reached normal values.

DISCUSSION

The results in the first two cases presented duplicate the findings of Shohl and Butler,[3] namely, that calcification of rachitic cartilage can be demonstrated by x-ray when citrate in adequate amounts is fed to rachitic infants despite the fact that the concentrations of calcium and phosphorus remain below the levels considered to be necessary for deposition of bone salts. Although it seems probable that the quantity of citrate administered to these infants would alter the solubility of calcium in the intestinal contents, thus promoting increased absorption of both calcium and phosphorus, the findings actually show no evidence of such an effect. There is no rise of the concentration of serum phosphorus nor any increase in the urinary excretion of phosphorus following citrate therapy. Even more striking is the significant decrease in the concentration of serum calcium during the initial response to citrate therapy. The possibility of an increase in the diffusible fraction of serum calcium in the form of a calcium citrate complex must also be discarded since the concentration of citrate in the serum is actually not elevated following citrate therapy but remains at about 2 mg. per cent. The rapid decrease of serum calcium levels when citrate therapy is begun with persistently low concentrations of serum phosphorus suggests that the effect of citrate is to increase the calcifiability of the rachitic cartilage so that calcium salts are deposited more rapidly than the rate of intestinal absorption of calcium. Since balance studies were not made it is impossible to say whether increased intestinal absorption of calcium and phosphorus did result from citrate feeding. However, if it

did occur, the increased absorption was not great enough to keep pace with the rate of skeletal uptake of these ions. This situation resembles that seen in certain patients with hyperparathyroidism following removal of the hyperfunctioning parathyroid tissue.[14] When increased parathyroid function is associated with considerable decalcification of bone and high concentrations of serum alkaline phosphatase, which is believed to indicate stimulation of osteoblastic activity, successful removal of the hyperfunctioning parathyroid tissue is followed by a rapid decrease of the concentration of serum calcium to subnormal levels while the serum phosphorus levels remain low. During this period large amounts of calcium may have to be given to prevent symptoms of tetany and x-rays of the bones show evidences of rapid recalcification of the demineralized bone. When the bone is remineralized the concentrations of serum calcium and phosphorus rise to the normal range. It would seem that the properties of the decalcified bone are such that as soon as the excess parathyroid hormone disappears from circulation the skeleton takes up calcium and phosphorus at so rapid a rate that the concentrations of these ions in the body fluids decrease despite a normal or high intake.

The possibility that citrate may influence the capacity of rachitic bone to take up calcium salts by virtue of an effect upon calcifiability of cartilage and bone matrix is of considerable theoretical interest since one of the major unsolved problems in bone physiology is the question of the nature of the biochemical changes involved in the precipitation of bone salts in the organic matrix. It is obvious that the properties of the organic matrix itself are fundamental although the concentrations of calcium and phosphorus in the body fluids play an important role. The mode of action of orally administered citrate in increasing the rate of uptake of bone salts by the rachitic bone cannot be the result of an increased concentration of citrate in the body fluids since determinations of serum citrate show no consistent rise until vitamin D is given. The absorbed citrate is evidently metabolized rapidly, perhaps in the intestinal wall and liver, so that the concentration of citrate in extracellular fluid is not persistently raised. Hamilton and Dewar[1] originally thought that sodium salts of organic acids might have an antirachitic effect due to the production of a metabolic alkalosis. The fact that the salts of organic acids other than citrate and tartrate were not antirachitic in the rat caused Shohl[2] to doubt this hypothesis. The citrate mixtures used in the treatment of rachitic infants do supply a large excess of sodium after the citrate has been metabolized. That alkali excess alone could produce the healing of rickets seems doubtful and some more specific metabolic action of citrate may be involved. Since citrate in its metabolism is transformed through a series of organic acids of which the first stages are oxalsuccinic acid and α-ketoglutaric acid,[15] further investigation is indicated to see whether administration of these tri- or dicarboxylic acids in the citric acid cycle influences the uptake of calcium by bone.

In the third case studied another manifestation of citrate therapy is seen. In this case of early rickets without marked proliferation of rachitic cartilage healing of the rachitic proc-

ess by citrate administration was accompanied by a gradual return of the serum phosphorus level to normal values while the concentrations of calcium remained at the lower limits of normal. As the serum phosphorus level rose the serum alkaline phosphatase activity progressively decreased. This response to citrate therapy resembles the response to vitamin D treatment. Park[4] has remarked that in the citrate treatment of rickets, healing first occurs without increase of the levels of serum phosphorus and calcium but as treatment is continued the concentrations of these ions finally rise to normal. It is presumed that this latter change occurs when the uptake of calcium and phosphorus by bone is balanced by the rate of absorption of calcium and phosphorus from the intestinal tract. Rominger[5] has also reported normal concentrations of calcium and phosphorus in the serum of rachitic infants fed large quantities of sodium citrate for periods of three to five weeks. It is not known, however, whether prolonged citrate therapy can completely substitute for vitamin D in the prevention and treatment of rickets. Since vitamin D treatment of rachitic infants results in an increase in the concentration of the serum citrate and the urinary excretion of citrate[12] it is intriguing to speculate on the interrelation of vitamin D and citrate metabolism although the mechanism of this effect is not yet explained.

SUMMARY

Observations were made on three rachitic infants during the course of treatment with a citrate mixture without vitamin D. The studies included determinations of calcium, phosphorus, citrate, and phosphatase in the serum and the daily excretions of calcium, phosphorus, and citrate in the urine. X-rays of the long bones were taken at intervals so that the evidences of deposition of bone salt in the rachitic cartilage could be correlated with the concentrations of calcium and phosphorus in the serum. The citrate solution consisted of an equimolar mixture of citric acid and trisodium citrate which was added to the milk feedings in amounts ranging from 30 to 60 mM. of citrate per day.

In two infants with advanced florid rickets citrate administration resulted in a rapid drop of the concentrations of serum calcium to hypocalcemic levels while the serum phosphorus values remained low. Deposition of bone salt in the rachitic cartilage was evident by x-ray during the period in which the concentrations of calcium and phosphorus in the serum were below the normal range and Ca × P ratios were less than 30. The urinary excretion of calcium remained low during the period of citrate treatment and the urinary excretion of phosphorus was unchanged. The concentrations of citrate in the serum were not consistently increased during citrate treatment but rose after vitamin D was given.

A third infant with early rickets and tetany showed a somewhat different pattern of response to citrate feedings. The serum calcium level which had risen following high calcium intake decreased somewhat when citrate was given but the concentration of phosphate and of citrate rose to normal values while the alkaline phosphatase activity in the serum decreased. X-rays of the bones showed normal

growth and calcification during the period of citrate therapy without vitamin D.

It is suggested that the antirachitic effect of citrate feeding is not simply due to the formation of a diffusible calcium citrate complex in the intestinal contents, nor in the extracellular fluids, but that there is a local action upon proliferating cartilage and bone matrix resulting in increased calcifiability. An analogy is drawn between the sequence of events following citrate feeding to rachitic infants and that seen in patients with decalcification of the skeleton due to hyperparathyroidism when the hyperfunctioning parathyroid tissue is removed. In both instances mineralization of the skeleton is associated with decreased levels of calcium and phosphorus in the serum.

In one patient of this series, however, a 2-month-old infant with early rickets, citrate feeding seemed to be a more complete substitute for vitamin D. While on citrate therapy the levels of serum phosphorus and of citrate rose to normal; the alkaline phosphatase activity of the serum decreased; and bone x-rays showed normal ossification. This is another suggestion of an interrelationship between citrate metabolism and the physiological effects of vitamin D.

We are indebted to Dr. Edwards A. Park not only for the inspiration which caused us to embark on researches concerning problems of calcification but also for advice and assistance in the prosecution of these studies.

REFERENCES

1. Hamilton, B., and Dewar, M. M.: Effect of Citrate and Tartrate on Experimental Rickets, Am. J. Dis. Child. **54:** 548, 1937.
2. Shohl, A. T.: The Effect of the Acid-base Content of the Diet Upon the Production and Cure of Rickets With Special Reference to Citrates, J. Nutrition **14:** 169, 1937.
3. Shohl, A. T., and Butler, A. M.: Citrates in the Treatment of Infantile Rickets, New England J. Med. **220:** 515, 1939.
4. Eliot, M. M., and Park, E. A.: Brennemann's Practice of Pediatrics, vol. 1, ch. 36, Hagerstown, 1948, W. F. Prior Co., Inc.
5. Rominger, E.: Ueber Versuche zur Rachitisheilung und Verhütung ohne Anwendung von Licht oder D-Vitamin, Arch. f. Kinderheilk. **131:** 53, 1944.
6. Heinz, E., Müller, E., and Rominger, E.: Citronensäure und Rachitis, Deutsche Ztschr. f. Kinderheilk. **65:** 101, 1947.
7. Heinz, E., Müller, E., and Rominger, E.: Citronensäure und Rachitis, Deutsche Ztschr. f. Kinderheilk. **65:** 637, 1948.
8. Kramer, B., and Tisdall, F. F.: A Simple Technique for the Determination of Calcium in Small Amounts of Serum, J. Biol. Chem. **47:** 475, 1921.
9. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66:** 375, 1925.
10. Natelson, S., Pincus, J. B., and Lugovoy, J. K.: Microestimation of Citric Acid: a New Colorimetric Reaction for Pentabromacetone, J. Biol. Chem. **175:** 745, 1948.
11. Hawk, P. B., Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, ed. 12, Philadelphia, 1947, the Blakiston Co., p. 585.
12. Harrison, H. E., and Harrison, H. C.: Vitamin D and Citrate Metabolism: Studies on Rachitic Infants, Yale J. Biol. Med. **24:** 273, 1952.
13. Malmberg, N.: Occurrence and Significance of Early Periosteal Proliferation in the Diaphyses of Premature Infants, Acta pediat. **32:** 626, 1945.
14. Cope, O., and Hamlin, E.: Progress in Clinical Endocrinology, edited by Samuel Soskin, New York, 1950, Grune & Stratton, p. 102.
15. Martius, C., and Lynen, F.: Probleme des Citronensäurecyclus, Advances in Enzymology **10:** 167, 1950.

EFFECT OF PREGNANCY UPON THE IMMUNITY OF MICE VACCINATED AGAINST ST. LOUIS ENCEPHALITIS VIRUS

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DURING the 1930's, while a member of Dr. Park's house staff, I became interested in investigations of certain infectious diseases of infancy. Dr. Park's interest and encouragement made possible a period of study in virology and bacteriology at the Rockefeller Institute for Medical Research. One of the investigations carried out during my stay at the Institute concerned the effect of pregnancy upon immunity to viral infections. It has become clear in recent years that pregnancy may adversely affect resistance of human beings to poliomyelitis virus. Along similar lines, Shwartzman has shown that cortisone greatly reduces the resistance of animals to infection with poliomyelitis virus. In view of these observations, it may be of interest to report here the studies which I made regarding the effect of pregnancy upon the immunity of mice vaccinated against the St. Louis virus. The data presented below were published in April, 1939, in Vol. 69 of *The Journal of Experimental Medicine* (pp. 533-543).

Swiss mice are uniformly susceptible to intranasal or intracerebral injection of St. Louis encephalitis virus. However, when the virus is injected subcutaneously it enters the general circulation but does not multiply in the brain. It produces no lesions in the nerve cells and causes no symptoms of encephalitis. However, such subcutaneous injection produces a strong immunity against subsequent intracerebral injection of the virus.[1, 2]

The mechanism by which vaccination renders the brain cells immune is not known. During the course of investigations designed to study this matter, the question of the influence of pregnancy upon acquired immunity arose. Experiments were planned to determine whether pregnancy affected in any way the immunity induced by vaccination with the St. Louis virus.

MATERIALS AND METHODS

Mice.—All mice employed were of the selected Swiss strain. They are uniformly susceptible to St. Louis encephalitis virus inoculated intracerebrally or intranasally. In all experiments the mated females and their virgin controls were of the same age.

Virus.—The virus used throughout was St. Louis encephalitis virus, strain 3. Virus suspensions were prepared in the following manner: The brain of a mouse prostrate with encephalitis was removed under sterile conditions and ground in a mortar. The emulsion of brain tissue was then diluted with ten times its weight of hormone broth of pH 8.0. After thorough mixing the suspension was centrifuged at 1,000 r.p.m. for 5 minutes and the supernatant made up in serial tenfold dilutions in broth.

Vaccination.—The mice were vaccinated with one subcutaneous injection of 0.5 c.c. of a 1:1,000 dilution of virus in broth. On each occasion that the virus was used for vaccination it was titrated by intracerebral injection into virgin female Swiss mice. These titrations showed that the amount of virus used for vaccination was approxi-

mately 15,000 times the minimal lethal intracerebral dose. The subcutaneous injection of this quantity of virus never caused encephalitis.

Immunity Tests.—The immunity of the vaccinated mice was tested by intracerebral inoculation of the virus. All mice inoculated were under light ether anesthesia; each received 0.03 c.c. of the virus appropriately diluted in broth. The immunity tests were carried out 2 weeks after vaccination in all experiments except Experiment 7. On each occasion that the virus was used to test immunity, it was titrated by intracerebral injection into unvaccinated virgin mice. These titrations showed that

before the end of the experiment. The usual period of gestation of these mice was about 19 days. Mice failing to deliver litters 6 weeks after removal from the mating box were considered as nonpregnant. In one experiment some of the mated mice died a few days before the end of gestation. In these cases the presence of pregnancy was established by autopsy.

Autopsy Findings.—Practically all of the mice dying following intracerebral resistance tests developed typical symptoms of encephalitis. In the few doubtful cases the cause of death was proved to be encephalitis by histologic examination and by intracerebral inoculation of the suspected brains into mice.

TABLE I. SUSCEPTIBILITY OF UNVACCINATED PREGNANT AND UNVACCINATED VIRGIN MICE TO ST. LOUIS ENCEPHALITIS VIRUS

MICE	DILUTION OF VIRUS INJECTED INTRACEREBRALLY (0.03 C.C. OF VIRUS TO EACH MOUSE)			
	10^{-5}	10^{-6}	10^{-7}	10^{-8}
Unvaccinated virgin	4/4*	4/4	3/4	0/3
Unvaccinated pregnant†	3/3	3/3	2/3	0/3

*4/4 = 4 of 4 injected mice died of encephalitis.
†These mice delivered litters 1 to 3 days after inoculation of the virus.

TABLE II. IMMUNITY OF UNMATED MICE INDUCED BY VACCINATION WITH ST. LOUIS VIRUS

MICE	DILUTION OF VIRUS INJECTED INTRACEREBRALLY (0.03 C.C. OF VIRUS TO EACH MOUSE)						IMMUNITY INDUCED BY VACCINATION
	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	
Vaccinated virgin	1/7*	0/8	1/8	0/8	—	—	10,000 intracerebral M.L.D.
Unvaccinated virgin (controls)	—	—	4/4	8/8	8/8	2/8	

*1/7 = 1 of 7 mice injected died of encephalitis.
— = dilution not tested.

each vaccinated mouse tested for immunity received approximately 500 intracerebral M.L.D. of virus.

Mating.—Virgin females 2½ to 3 months old were chosen for mating. One male was mated to 5 females. As the females became pregnant, they were removed from the mating box to a separate jar. The date of delivery of the litter was recorded in each instance. Unless otherwise noted each litter was kept with its mother throughout the experiment.

Unmated Controls.—In each experiment a number of females were set aside as virgin controls. These animals were litter mates of those chosen for mating.

Determination of Pregnancy.—In most instances the pregnant mice delivered litters

EXPERIMENTAL

Susceptibility of Unvaccinated Virgin and Pregnant Mice to St. Louis Encephalitis Virus

Virgin mice are very susceptible to intranasally or intracerebrally inoculated St. Louis virus.[1, 2] Numerous titrations of the virus in virgin Swiss mice 1 to 3 months old have shown that intracerebral inoculation of 0.03 c.c. of a 1:1,000,000 dilution of virus is practically always fatal. The same quantity of a 1:10,000,000 dilution of virus kills about two-thirds of the

mice injected. Table I shows that unvaccinated pregnant females exhibit the same degree of susceptibility to the virus as do unvaccinated virgin mice. It appears that the intracerebral minimal lethal dose of St. Louis virus is the same for the unvaccinated pregnant female as it is for the unvaccinated virgin female Swiss mouse.

Immunity Induced in Virgin Mice by Vaccination With St. Louis Virus

It has already been reported that within one week following vaccination the great majority of virgin Swiss mice become immune to 10,000 or more intracerebral minimal lethal doses of St. Louis encephalitis virus.[1, 2] The immunity remains at this high level about 6 weeks, after which it begins to decline. Table II shows the degree of immunity exhibited by virgin female mice when tested 2 weeks after vaccination.

Influence of Pregnancy Upon Immunity Induced by Vaccination

It appears from the data already presented that pregnancy does not render unvaccinated Swiss mice either more or less susceptible to the St. Louis virus than are unvaccinated virgin mice. The experiments described below were planned to determine whether pregnant mice become immune following vaccination with the virus in the same manner as virgin mice.

Vaccination Late in Pregnancy.—

Experiment 1.—In this experiment the immunity induced by vaccination of mice during the last few days of pregnancy was compared with the immunity which follows vaccination of their unmated litter mates.

Twenty-eight female Swiss mice, 2½ months old, were divided into two groups, each consisting of 14 animals. Litter mates were equally distributed between the two groups. One group was mated with males of the same strain, while the other was set aside as unmated controls. All the mated females became pregnant and were not disturbed until 1 to 4 days before the end of the nineteenth day of the gestation period. At this time they were vaccinated subcu-

TABLE III. EFFECT OF PREGNANCY UPON IMMUNITY WHEN VACCINATING DOSE IS ADMINISTERED NEAR END OF PREGNANCY

IMMUNITY OF PREGNANT MICE* FOLLOWING VACCINATION			IMMUNITY OF UNMATED MICE FOLLOWING VACCINATION	
VACCINATED PREGNANT MOUSE NO.	TIME OF VACCINATION DAY OF PREGNANCY	FATE AFTER INTRACEREBRAL TEST FOR IMMUNITY (500 M.L.D. OF VIRUS)	VACCINATED UNMATED MOUSE NO.	FATE AFTER INTRACEREBRAL TEST FOR IMMUNITY (500 M.L.D. OF VIRUS)
1	18th	Died of encephalitis	1	Remained well
2	17th	Died of encephalitis	2	Remained well
3	17th	Died of encephalitis	3	Remained well
4	16th	Died of encephalitis	4	Remained well
5	18th	Died of encephalitis	5	Remained well
6	18th	Remained well	6	Remained well
7	16th	Died of encephalitis	7	Remained well
8	18th	Died of encephalitis	8	Remained well
9	17th	Died of encephalitis	9	Remained well
10	16th	Died of encephalitis	10	Remained well
11	16th	Died of encephalitis	11	Remained well
12	16th	Died of encephalitis	12	Died of encephalitis
13	16th	Died of encephalitis	13	Remained well
14	16th	Died of encephalitis	14	Remained well

Mortality of vaccinated pregnant mice = 93 per cent (13/14); mortality of vaccinated unmated mice = 7 per cent (1/14).

*Duration of pregnancy is 19 days in these mice.

taneously with 0.5 c.c. of a 1:1,000 dilution of St. Louis encephalitis virus. That is, the pregnant mice were vaccinated 15 to 19 days after conception. By titration of the virus used for vaccination it was estimated that the vaccinating dose employed was about 15,000 intracerebral M.L.D. Vaccination did not seem to interfere with the normal course of pregnancy; all the pregnant mice delivered normal litters 1 to 3 days after vaccination. The unmated mice were vaccinated at the same time as the pregnant animals, and with the same dose of virus. Two weeks after vaccination the immunity of both parturient and unmated mice was tested by intracerebral inoculation of about 500 M.L.D. of St. Louis encephalitis virus.

A summary of this experiment is recorded in Table III. The mice vaccinated late in pregnancy failed to develop sufficient immunity to enable them to withstand 500 M.L.D. of the virus. Thirteen of the 14 died of encephalitis following the test inoculation of virus, a mortality rate of 93 per cent. In contrast, only 1 of the 14 vaccinated unmated mice died after the intracerebral administration of the virus, a mortality rate of 7 per cent. Calculation of the standard error[3] indicates that this difference in mortality is probably not an accidental one. The result obtained might be expected to occur by chance much less frequently than one time in 100 ($P = < 0.01$).

When the offspring of the parturient vaccinated females became 10 to 13 days old, their immunity against intranasal instillation of St. Louis virus was tested. Ninety-two of 98 of the infant mice inoculated with 100 intranasal M.L.D. of virus died of encephalitis.

Experiment 1 a.—This experiment was carried out in exactly the same manner as Experiment 1. The result was practically identical. Twelve of 13 mice vaccinated 1 to 4 days before the end of pregnancy died of encephalitis after the intracerebral immunity test, a mortality rate of 92 per cent.

As before, the great majority of the vaccinated unmated mice were immune; only 2 of 15 (13 per cent) failed to withstand the test dose of virus. Again $P = < 0.01$.

The offspring of these vaccinated mothers also showed little evidence of immunity. Of the 80 young mice tested 75 died of encephalitis after receiving 100 intranasal M.L.D. of virus.

Vaccination During Middle Third of Pregnancy.—

The effect of vaccinating pregnant mice during the middle third of the gestation period was next studied as described in Experiment 2. The result indicated that the immunity induced by vaccination of mice at this stage of pregnancy was also diminished.

Experiment 2.—This experiment was conducted in the same manner as those already described except that the pregnant mice were vaccinated earlier in the gestation period, that is, 7 to 11 days after the onset of their pregnancy. Two weeks after vaccination the immunity of the unmated and of the parturient mice was tested by intracerebral inoculation of approximately 500 M.L.D. of virus.

Following this test dose of virus, 9 of 18 vaccinated pregnant mice died of encephalitis, a mortality rate of 50 per cent. As before, the vaccinated unmated mice proved to be immune, only 1 of 15 (7 per cent) died of encephalitis ($P = < 0.01$).

Vaccination Early in Pregnancy.—

Experiment 3.—In this experiment 22 mice were vaccinated during the first 4 days of pregnancy. Their immunity, together with that of vaccinated unmated controls, was tested 2 weeks after vaccination.

The response to vaccination was found to be depressed even very early in the gestation period. Eleven of the 22 vaccinated pregnant mice (50 per cent) died of encephalitis after intracerebral inoculation of approximately 500 M.L.D. of virus as compared with only 1 of 14 (7 per cent) of the vaccinated unmated mice ($P = < 0.01$).

Vaccination During the Puerperium.—

The experiments described above indicated that pregnancy inhibits or depresses the immunity which is produced by vaccination. It seemed important to learn whether the power to acquire immunity against the virus was regained after the mice had delivered their young. Accordingly, the response to vaccination carried out at various intervals after the end of pregnancy was studied in Experiments 4, 5, and 6 described below. It was found that the degree of immunity exhibited by the vaccinated puerperal mice during the first 2 weeks after delivery of their young was less than that of vaccinated virgin mice. However, mice vaccinated 7 weeks after the end of pregnancy appeared to withstand the intracerebral inoculation of 500 M.L.D. of the virus as well as did vaccinated virgin mice. Apparently at this time the mice which have reared young have regained at least in part their ability to acquire immunity against the virus. Fig. 1 summarizes these results.

Vaccination During the First 2 Days After the End of Pregnancy.—

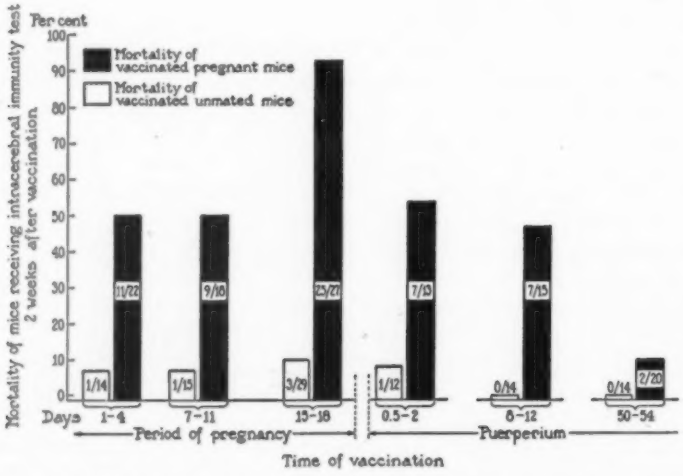

Fig. 1.—Effect of pregnancy upon immunity produced by vaccination against St. Louis encephalitis virus.

Experiment 4.—Thirteen Swiss mice were vaccinated against St. Louis virus within the first 48 hours after they had delivered litters. At the same time 12 virgin females were vaccinated. Two weeks later the immunity of all the mice was tested in the usual way against intracerebrally inoculated St. Louis encephalitis virus.

Seven of the 13 vaccinated puerperal mice (54 per cent) died of encephalitis while only 1 of the 12 vaccinated virgin mice (8 per cent) failed

to survive the test virus ($P = < 0.01$).

Vaccination During the Second Week After the End of Pregnancy.—

Experiment 5.—This experiment was performed in the same manner as Experiment 4, except that the mice which had borne litters were vaccinated later in the puerperal period; that is, 8 to 12 days after delivery of their young.

Seven of 15 (47 per cent) of the mice vaccinated during the puerperium died of encephalitis following the intracerebral test inoculation of 500 M.L.D. of virus. None of 14 vaccinated unmated mice failed to survive the immunity test ($P = < 0.01$).

None of the 14 vaccinated virgin controls died of encephalitis and only 2 of the 20 vaccinated mothers (10 per cent). This difference is probably due to chance ($P = 0.21$).

Effect of Pregnancy Upon Immunity Established by Vaccination Before Mating.—

It seems clear from the data presented that mice vaccinated during pregnancy are in some manner prevented from developing strong immunity against the St. Louis virus. The effect of pregnancy upon immunity already well established before the onset of gestation was investigated in Experiment 7. The result of Experiment 7 (summarized in Table IV) shows that pregnancy brings about a reduction of the immunity acquired before mating.

TABLE IV. EFFECT OF PREGNANCY ON THE IMMUNITY ESTABLISHED BY VACCINATION BEFORE MATING

MICE	TIME MATED	TIME OF INTRACEREBRAL IMMUNITY TEST	MORTALITY FOLLOWING INTRACEREBRAL IMMUNITY TEST (500 M.L.D. OF VIRUS)
Vaccinated virgin	—	1 wk. after vaccination	0/11* (0 per cent)
Vaccinated virgin	—	23 da. after vaccination	2/16 (13 per cent)
Vaccinated, then mated (pregnant)	1 wk. after vaccination	23 da. after vaccination (16 da. after mating)	12/18† (67 per cent)

*0/11 = None of 11 injected mice died of encephalitis.
†Of the 6 survivors in the pregnant group, 3 had been pregnant only 1 or 2 days when given the test virus.

Vaccination 7 Weeks After the End of Pregnancy.—

Experiment 6.—In this experiment the mice were vaccinated 7 weeks after they had delivered their litters; that is, 4 weeks after weaning of their young.

Twenty female Swiss mice were mated with 4 males, while 14 of their litter mates were kept as virgin controls. All the mated females delivered litters 19 to 23 days after mating. Fifty to 54 days after delivery the young were weaned and removed from their mothers and discarded. About 4 weeks later (more than 7 weeks after delivery) the mice which had reared young and the virgin controls were vaccinated against St. Louis virus in the usual way. Two weeks later the vaccinated mice were inoculated intracerebrally with about 500 M.L.D. of St. Louis encephalitis virus.

Experiment 7.—Forty-six female Swiss mice were vaccinated with St. Louis virus in the manner previously described. One week later 11 of them were chosen at random and their immunity tested against approximately 500 intracerebral M.L.D. of virus. All of these mice survived the immunity test and it was therefore assumed that the remaining 35 vaccinated mice were also immune. One week after vaccination 19 of these latter animals were mated to 5 males of the same strain while 16 were set aside as virgin controls. Sixteen days later (23 days after vaccina-

tion) the males were removed and the immunity of the mated and virgin vaccinated females was tested by intracerebral inoculation of approximately 500 M.L.D. of virus. Of the 19 mated mice, 18 either delivered litters before the end of the experiment or were found by autopsy to be within 3 or 4 days of term when death from encephalitis occurred.

Following the inoculation of the test virus, 12 of the 18 pregnant mice (67 per cent) died of encephalitis as contrasted with only 2 of 16 (13 per cent) of the vaccinated unmated animals ($P = < 0.01$). It is of interest to note that of the 6 vaccinated pregnant mice which survived 3 had been pregnant only 1 or 2 days and 2 only 10 days when the immunity test was done. All the vaccinated pregnant mice which died of encephalitis had been pregnant 14 to 16 days when they received the test virus.

DISCUSSION

There are certain indications in the literature that various physiologic factors may influence the reaction of animals to virus infections. For example, it seems clear that the age of the animal may be important in this regard. It has been shown by Sabin[4] that old mice are immune to exceedingly large doses of vesicular stomatitis virus injected into the leg muscles, while young mice develop a fatal encephalomyelitis. Sabin stated that in young mice the virus multiplies at the site of inoculation and invades the sciatic nerve and spinal cord, while in old mice this invasion of the central nervous system does not take place.

It has been reported by Sprunt[5] that pregnancy alters the reaction of the tissues of the rabbit to the virus of infectious myxomatosis. Sprunt reported that following intradermal inoculation of this virus more extensive lesions occur in the spleens of pregnant animals than in unmated ones, and that secondary lesions are found uniformly in the lungs of pregnant animals, while only an occasional lesion is found in the lungs of nonpregnant rabbits. On the other hand the skin of the pregnant animals seems to be less affected by the virus than is the case in the nonpregnant rabbits.

The experiments described in the present communication show that pregnancy does not increase the susceptibility of mice to the St. Louis encephalitis virus, but pregnancy does very definitely diminish the response to vaccination with the virus. This depression of the ability to acquire immunity is most marked late in pregnancy, but it is also demonstrable very early in pregnancy as well as during the first 2 weeks post partum. However, the immunity response is not permanently reduced by pregnancy. When mice are vaccinated 7 weeks after the end of pregnancy, it is found that their ability to acquire immunity has been regained, at least in part.

It is of interest to note that the offspring of the mice vaccinated during the course of pregnancy are not immune to the virus. Very few of these young mice were able to withstand the administration of 100 intranasal M.L.D. of the virus.

It should be emphasized that pregnancy not only inhibits the development of immunity but that it also adversely affects an already well-established immunity. This would suggest that pregnancy exerts its influence not by altering the virus injected as the vaccinating agent but rather that

it affects in some manner the tissues which are made immune by vaccination. By what mechanism the state of pregnancy brings about this alteration is not known. Pregnancy is accompanied by very profound physiologic changes in the animal. It seems likely that one or more of these metabolic changes are responsible, although it is impossible at the present time to say which are involved. Experiments designed to study some of these factors, such as the hormones which exert a great influence on the course of pregnancy, are being undertaken.

SUMMARY

1. Virgin and pregnant Swiss mice are equally susceptible to intracerebral inoculation of St. Louis encephalitis virus.

2. Following subcutaneous vaccination with the St. Louis virus, the great majority of virgin Swiss mice become immune to subsequent intracerebral injection of 10,000 M.L.D. of the virus.

3. The majority of mice vaccinated during pregnancy do not become immune to even as little as 500 intracerebral M.L.D. of the virus. The depression of the ability to acquire immunity against the virus is most marked when the vaccination is carried out late in pregnancy, but it is also demonstrable when the mice are vaccinated early in the gestation period and during the first 2 weeks post partum. At 7 weeks post partum the response to vaccination is more nearly like that of virgin mice.

4. Pregnancy not only interferes with the development of acquired immunity but it also diminishes a previously established immunity.

5. Offspring of the mice vaccinated during pregnancy are not immune to 100 M.L.D. of virus.

REFERENCES

1. Webster, L. T.: J. Exper. Med. **68**: 111, 1938.
2. Hodes, H. L., and Webster, L. T.: J. Exper. Med. **68**: 263, 1938.
3. Topley, W. W. C., and Wilson, G. S.: Principles of Bacteriology and Immunity, Baltimore, 1937, William Wood and Co., p. 774.
4. Sabin, A. B., and Olitsky, P. K.: J. Exper. Med. **66**: 35, 1937.
5. Sprunt, D. H.: J. Exper. Med. **56**: 601, 1932.

CONGENITAL OBLITERATION OF THE BILE DUCTS

With Particular Reference to Dietotherapy

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THE present report deals with a case of congenital obliteration of the bile ducts with an unusually long survival (nine years 3 months) in which it was possible to carry out balance studies designed to throw light on the absorption of fat in this condition.

CASE REPORT

A. G., a Negro male infant, was born in Kings County Hospital, Feb. 21, 1942; his birth weight was 6 pounds 2 ounces. The early days of life were uneventful and the infant was discharged from the hospital on a milk formula; orange juice and oleum percomorphum (10 drops a day) being added shortly thereafter. Jaundice and pale stools were first noted by the parents at the age of 2 weeks; the jaundice gradually deepened and for this reason he was readmitted to the hospital at 4 months of age. Physical examination at this time revealed a fairly well-nourished infant weighing 11 pounds 10 ounces with moderate icterus of the skin and sclerae. There were clinical evidences of rickets: craniotabes, costochondral beading, and enlargement of the wrists. The anterior fontanel was very large (2 x 3 inches) as was the posterior fontanel (1 x 1 inches). The liver edge was palpable 2 fingerbreadths below the costal margin; the spleen was not felt. The remainder of the physical examination was negative. The following laboratory examinations carried out at that time are of interest. The urine was dark, positive for bile, and negative for urobilinogen. The stools were clay colored and negative for bile. The red blood count was 3.95 million; hemoglobin 10.5 grams; white blood count 9,200 with a normal differential count. Serological tests for syphilis were negative. There was a positive direct van den Bergh reaction. Icterus index was 80 units. Serum calcium was 8.8 mg. per cent, phosphorus 2.7 mg. per cent, and alkaline phosphatase 18.1 Bodansky units. Bleeding and clotting times were normal. Roentgenograms of the long bones revealed typical rachitic changes at the costochondral junctions.

A provisional diagnosis of congenital atresia of the bile ducts was made and laparotomy was performed at 6 months of age. This revealed complete absence of the gall bladder, the hepatic and common ducts. A hepatojejunostomy was attempted. The baby made an uneventful recovery from the operation and was discharged from the hospital on the sixteenth postoperative day on a normal diet with the addition of vitamin K, bile salts, Drisdol 20 drops, and Vipenta 45 drops, making a total of 9,500 international units of vitamin D per day.

At the age of 20 months, he was again admitted to the hospital for the treatment of a severe bronchiolitis. At this time, he was able to sit, but could not stand, walk, or talk. Jaundice was intense, and although this was the only occasion that the prothrombin time was elevated, there

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was no evidence of bleeding. The liver and spleen were markedly enlarged to 4 fingerbreadths below the costal margin. There was no distention of the superficial veins of the abdomen, nor any evidence of ascites. For the first time it was noted that there was a moderate clubbing of the fingers. Although the calcium, phosphorus, and phosphatase determinations were much the same as on previous admissions, craniotabes was no longer present, the posterior fontanel had closed, and the anterior fontanel was much smaller, admitting only a finger tip. However, roentgenograms of the long bones showed an increase in demineralization and also an increase in the thinning of the cortices. There were large areas in the long axis of the bones which were cystic in appearance. There was a retardation in bone growth; in fact, it now appeared as though some bone atrophy had taken place.

During the succeeding eight years he was kept under close medical supervision, at Kings County Hospital, being followed regularly in the outpatient department and frequently being readmitted to the wards because of repeated respiratory infections and fractures of long bones which occurred as the result of relatively minor trauma. His physical growth and mental development were

Fig. 1.

Fig. 2.

Fig. 1.—Roentgenogram of arm of A. G. at 4 years of age, showing extreme osteoporosis and pathological fracture.

Fig. 2.—Roentgenogram of forearm of A. G. at 5½ years of age, showing rickets, extreme osteoporosis, and pathological fracture.

greatly retarded; the bone age only slightly so. Deformities of the long bones developed as the result of fractures. Evidences of rickets had been noted in the x-rays of the extremities as late as 5 years of age, but not thereafter. Osteoporosis was, however, extreme at all times. Icterus remained intense and the boy suffered considerably from pruritus, the skin being dry and scaly. Clubbing of the fingers continued to increase. Apart from the therapy for fractures and for acute respiratory infections efforts were made to provide him with a liberal vitamin D intake and to restrict fats in his diet. Significant laboratory findings are shown in Fig. 3.

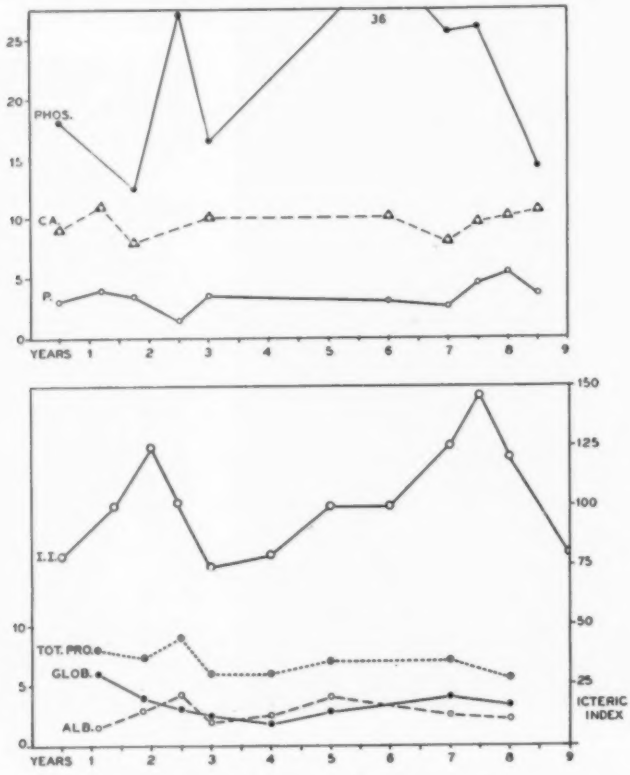


Fig. 3.—Blood chemical findings in A. G.

At the age of 8 years he was transferred to Bellevue Hospital for metabolism studies. Physical examination at this time showed a phlegmatic undersized boy who would sit all day with his legs crossed in tailor fashion and who spent much time scratching. He could walk with support but required encouragement to do so. He was found to have a mental age of 4 years. His weight was 29 pounds, height 36 inches. Abnormal findings on physical examination included intense icterus, most conspicuous in the sclerae. There was marked proptosis. The teeth had a greenish tint and were badly decayed with considerable gum hypertrophy. The thorax showed some evidence of a Harrison's groove with marginal flaring. Intermittent râles were heard over both lungs and there was a systolic heart murmur of ques-

tionable significance. The abdomen was large and protuberant, the liver edge being felt 4 fingerbreadths below the costal margin as a hard and nodular mass. The spleen, too, was readily palpable. No evidence of ascites was present. The extremities were thin and wasted; some bowing was present, and there was marked clubbing of the fingers and toes. Deformities of the right femur and left humerus were present at the site of previous fractures. Laboratory findings at this time showed a serum calcium of 11.5 mg. per cent, phosphorus 4.03 mg. per cent, and phosphatase 12.3 Bodansky units. A flat vitamin A curve was obtained with an oily preparation; there was, however, no clinical evidence of vitamin A deficiency.

The boy was kept in the hospital for three and one-half months during which time the metabolism studies described below were carried out. Following the administration of a liberal fat diet he gained weight and showed a marked improvement in his spontaneous activity. He was discharged from the hospital on April 17, 1950.

During his subsequent course he made periodic visits to Kings County Hospital, but was not under as close observation as had previously been the case. A physician who was unfamiliar with the results of the metabolism study discontinued the high fat diet. His weight gain was less satisfactory thereafter and his physical activity also declined.

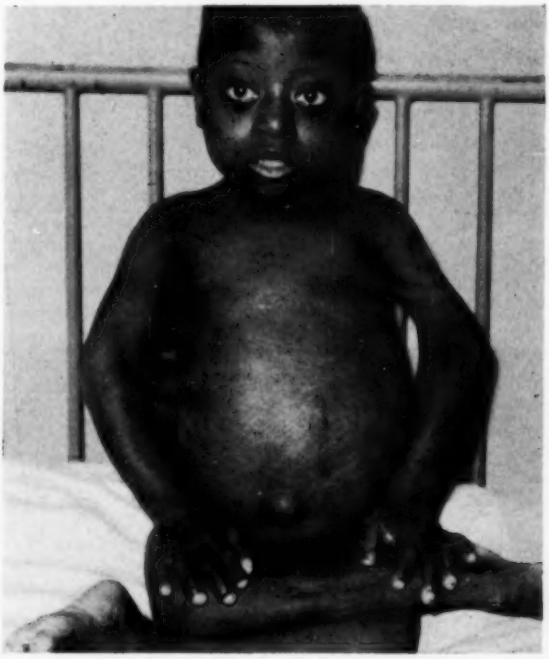


Fig. 4.—A. G. at 8 years of age.

In June, 1951, he was admitted to the surgical service of Kings County Hospital for treatment of a fracture. Shortly after admission he developed a severe bronchopneumonia complicated by marked abdominal distention and the sudden development of shock. Intestinal obstruction was suspected, but laparotomy could not

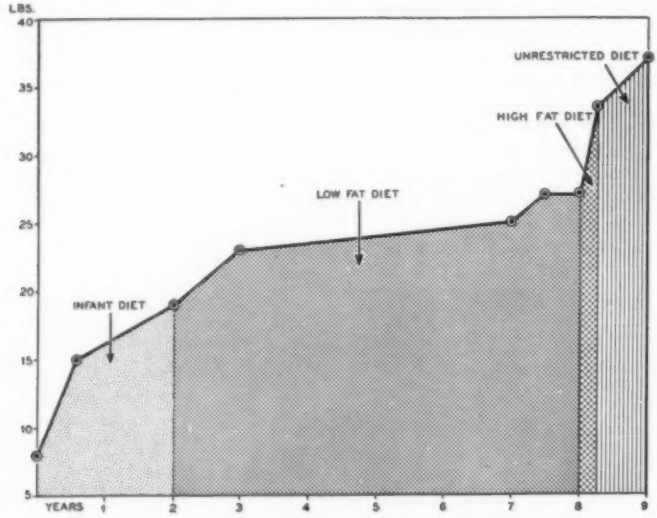
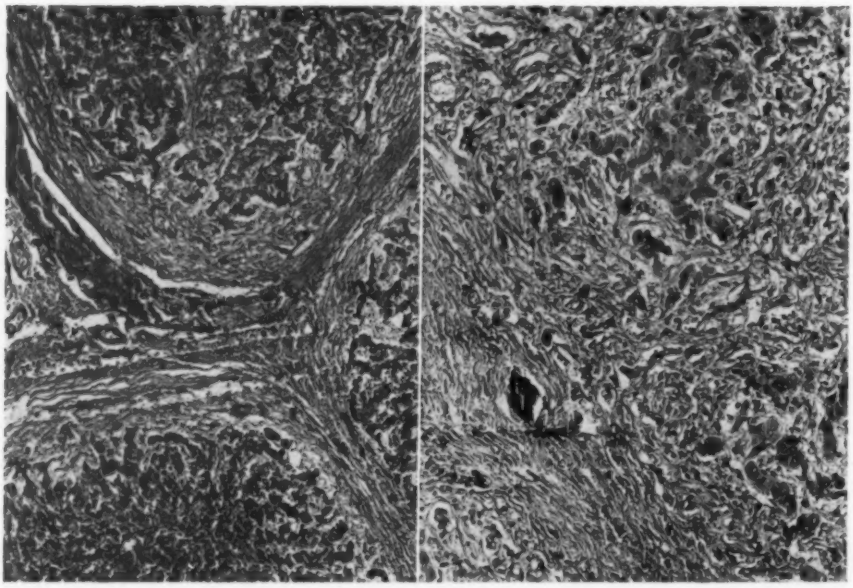


Fig. 5.—Weight curve of A. G. in relation to diet.



A. *B.*

Fig. 6.—*A*, Microscopic appearance of liver at autopsy, showing cirrhosis with agenesis of bile ducts. (×60.) *B*, Microscopic appearance of liver at autopsy, showing cirrhosis perilobular bile canaliculi and rare bile intrahepatic duct formation. (×80.)

be performed because of the severity of the shock, and death occurred within a few hours despite supportive measures on June 8, 1951.

An autopsy, for the report of which we are indebted to Dr. C. G. Burn, revealed emaciation, bronchopneumonia, a fibrous band which had caused ileal obstruction and fibrous peritoneal adhesions. Icterus was intense. There was marked splenomegaly. The bones* showed extreme osteoporosis; there was definite microscopic evidence of rickets in the form of occasional borders of osteoid along the trabeculae of the shaft.

Of particular interest were the findings in the liver and bile passages. A thorough dissection confirmed the complete absence of the gall bladder and extrahepatic ducts; the ampulla of Vater was located and only the pancreatic duct could be demonstrated. The liver was small, cirrhotic, dark brown to green in color, and studded throughout with variable sized nodules of parenchymal tissue. Focal zones of dark green to black due to bile stasis were observed. Multiple histological sections failed to reveal the presence of any extrahepatic bile ducts or atretic forms of bile ducts. At the usual sites dense collagenous scar tissue was found and a few small focal accumulations of lymphocytes were demonstrable within this tissue. Microscopic examination of the liver revealed numerous variable sized interlacing bands of dense collagenous fibrous tissue within the periportal areas which surrounded islands of hepatic cells. The liver lobules were variable in size, but the hepatic cells appeared well formed and lined the sinusoids in a regular manner. The intrahepatic bile ducts were absent except for an occasional well-formed bile duct lined by a low cuboidal epithelium. At the periphery of many lobules adjacent to the dense fibrous connective tissue strands of the periportal zones, a loosely arranged interlacing fibrous connective tissue was seen replacing many of the hepatic cells in which small irregular poorly developed and tortuous canaliculi were observed. Some of the canaliculi were lined with a swollen cuboidal type of epithelium while others were free of an epithelial lining. Many of the canaliculi contained inspissated bile in their lumina. Bile duct anastomosis between the liver parenchyma and the closely adherent loop of the jejunum could not be demonstrated.

*We wish to thank Drs. E. A. Park and R. H. Follis, Jr., for examining these bone sections.

METABOLIC OBSERVATIONS

The patient reported above was of particular interest to us because of the opportunity he afforded to study the steatorrhea resulting from absence of bile from the digestive tract. The role of bile in the absorption of fats has long been known and numerous observations[1-10] have demonstrated that fat absorption is greatly impaired in cases of biliary atresia, as much as 50 per cent of the ingested fat and often more than this being lost in the feces. The feeding policy generally followed in these cases has been to restrict dietary fat, on the reasoning that a food relatively useless from the point of view of absorption should be avoided and that unabsorbed fat might do harm. A fat-poor regimen has been thought to be beneficial for liver disease in general, even when unaccompanied by biliary obstruction.

Observations made by some of us in other forms of steatorrhea, namely, that seen in acute diarrhea,[11] in celiac disease,[12] in cystic fibrosis of the pancreas,[12] and in premature infants[13] had led us to question the value of restricting fat in these conditions; no evidence was found that fat even when given in large quantity was harmful, and definite evidence was obtained that absolute absorption of

fat was increased by its administration, the percentage absorption remaining virtually unaffected. We were interested to know if a similar situation prevailed in the case of biliary atresia. We were furthermore encouraged in this endeavor by the experiences of others with unrestricted fat diets[14, 15] in other forms of liver disease, namely, infectious hepatitis and cirrhosis. Balance studies were therefore carried out in our patient designed to ascertain: (a) the effect of varying the fat intake upon fat absorption, (b) the effect of homogenization of the administered fat, and (c) the effect of a surface active agent which had been reported to improve fat absorption in other forms of steatorrhea.[16]

The general procedures employed in these studies were as reported by us elsewhere.[12] To simplify the preparation of the stools for analysis a milk diet was employed, being supplemented by melted butter fat when a higher fat intake was desired. The homogenized feeding was prepared by means of a dairy homogenizer. In the period in which the surface active agent (Tween G1205*) was used, this substance was given orally with meals the quantity given being proportional to that of the fat of the feeding (1 part Tween to 40 parts fat). Metabolism periods were five days in length, the stools being marked at the beginning and end of the period by means of carmine. Fat analyses were carried out as described elsewhere.[12] Table I shows the results obtained.

*This material was supplied to us by the Atlas Powder Company through the courtesy of Dr. K. R. Brown.

DISCUSSION

It will be noted that increasing the fat intake from 63.2 to 168.8 grams per day caused a notable increase in the steatorrhea, the fat loss in the stool being more than doubled. It also appears that the fat absorbed by the child was likewise more than doubled, the percentage absorption showing negligible changes. The situation thus appeared to be altogether similar to that observed by us in other forms of steatorrhea. As measured by percentage absorption no evidence of lost tolerance was encountered on the high fat diet.

Table I. Fat Absorption Studies in Patient A. G.

DIET	FAT INTAKE GM./DAY	FECAL FAT GM./DAY	FAT ABSORBED	
			GM./DAY	% OF INTAKE
Evaporated milk	63.2	36.8	26.4	41.5
Evaporated milk + butter	168.8	90.0	78.8	46.6
Evaporated milk	63.2	37.2	26.0	41.0
Evaporated milk + butter	168.8	82.5	86.3	51.1
Evaporated milk + butter (homogenized)	168.8	82.0	86.8	51.5
Evaporated milk + butter + Tween G1205	168.8	77.1	91.7	54.3

Homogenization of the fat failed to produce any significant improvement in absorption. A slight and questionably significant improvement in absorption was, however, noted on the Tween period, comparable in magnitude to the improvement we have observed[17] in premature infants.

The patient A. G. was kept on a generous fat intake for many weeks,

during the metabolism studies just described. His appetite remained excellent. His spontaneous activities showed a marked increase and the weight curve shows a substantial rise at this time. The weight curve (Fig. 5) also demonstrates that weight gain was increased during those periods when fat intake was not restricted and a normal diet was allowed. Although we are not at this time* able to present evidence from more than a single case in favor of a liberalization of the fat intake in congenital biliary atresia, the present experience lends support to the belief that this form of steatorrhea is analogous to the other forms we have previously studied in that unabsorbed fat in the intestine is not to be feared. Restriction of this foodstuff deprives the patient of a valuable source of calories and of a food which may serve other functions as well. The fallacy of using the stools as a guide to feeding in digestive disturbances was clearly pointed out by Park[18] more than a quarter century ago.

Two other questions of interest are raised by our experience with the patient A. G.—the nature of the bone lesions in biliary atresia and the cause for the unusually long survival. The association of rickets with biliary atresia was stressed particularly by Gerstenberger[19] who believed that "hepatic rickets" represented a peculiar form of rickets resistant to vitamin D therapy. Subsequent work by Greaves and Schmidt[20] and by Heymann[21] demonstrated the importance of bile in the absorption of vitamin D, suggesting that "hepatic rickets" was in fact vitamin D deficient rickets conditioned by the difficulty in intestinal absorption of D. This point of view found support in the observations of Thoenes and Gruson[22] who were able to induce healing in such a case by means of intensive ultraviolet irradiation. That rickets is a common complication of biliary atresia is beyond question; also that it can be prevented if a sufficiently large dose of D is given by mouth or if D is given parenterally. Florid rickets was present in our patient during infancy. It was not adequately controlled by generous dosage of vitamin D and, although clinical and roentgenological evidences were no longer detectable after the age of 5½ years, definite evidence of rickets was found at autopsy. It is of interest that rachitic changes were found at autopsy only in the shaft; this is in accordance with the observations of Follis and associates[23] in rickets when seen in older children in whom rapid bone growth is no longer occurring. The rickets during the latter part of this child's life was not detectable by the calcium and phosphorus levels in the

*Since this was written we have had the opportunity to study a second case of congenital biliary atresia at different levels of fat intake. This infant, a girl of 6 months, was studied in three successive periods with the following results:

PERIOD	DIET	FAT INTAKE GM./DAY	FECAL FAT GM./DAY	FAT ABSORBED	
				GM./DAY	% OF INTAKE
I	Milk	24	17.4	6.6	27.5
II	Milk + butter	100	45.0	55.0	55.0
III	Milk	24	10.6	13.4	56.0

It is possible that the extremely low retention figure in period I represented incomplete recovery from a preceding infection. The virtual identity of the percentage absorption figure in periods II and III is quite in accord with our experience on patient A. G.

blood serum; an elevation of the alkaline phosphatase was, however, present.

Quite apart from the predisposition to rickets, it is clear that biliary atresia affects the bones. The degree of osteoporosis in our patient in his later years was extreme as contrasted with the minimal rickets present. Park[24] calls attention to the possibility that osteoporosis without rickets may develop in these cases and that great rarefaction of the skeleton is *regularly* found. The extreme rarefaction is apparently responsible for the tendency to spontaneous fractures. In the present instance we can do no more than point out that the findings in our patient support the view that biliary atresia leads to osteoporosis irrespective of rickets. One may speculate as to the underlying basis for such a relationship—whether it is due to the presence of some constituent of the bile or to the failure of some hepatic function is a matter which future work may decide.

The cause for the unusual longevity of our patient A. G. is a matter of considerable interest. We are not aware of any report in the literature in which a patient with biliary atresia has survived for such a long time. Stolkind[25] who reviewed the literature in 1939 reported on 276 cases of which only two lived as long as fifteen months. Recently, however, Ahrens and collaborators[26] reported prolonged survival (in one instance a patient still living at 6½ years) in cases with atresia of the intrahepatic bile ducts. They offered the suggestion that the absence of the intrahepatic ducts might limit pressure damage to the liver cells although admittedly the pressure from distended bile canaliculi would be present. The prolonged survival in our patient is in keeping with their observations, since intrahepatic ducts were virtually absent in him. However, before accepting their hypothesis it would seem that other possibilities which might make for prolonged survival should be mentioned. It may be pointed out that even in the group with intrahepatic duct atresia prolonged survivals have occurred only in recent years. We have furthermore gained the impression from talking to our colleagues who have unreported cases of biliary atresia under observation that prolonged survival is now not so rare, regardless of the nature of the malformation. The usual causes of death in biliary atresia have been two: (1) infections with marked toxicity which have often precipitated digestive disturbance and (2) hemorrhage. It seems not impossible that the advent of antibiotics and of vitamin K may have been responsible for prolonging life. Control of infection may serve not only to limit liver damage, but also to limit the serious digestive disorders caused by parenteral infections during infancy.

We are not in a position to make claims for therapeutic benefit from a liberal fat diet. More experience is obviously needed. Nevertheless the chemical and clinical observations here reported lend support to the view which has gained adherents in other forms of liver disease, namely, that fat restriction is unnecessary and fat administration without danger.

SUMMARY

1. A patient with atresia of the intrahepatic and extrahepatic bile passages is reported who survived for nine years.

2. Studies of fat absorption carried out at different levels of fat intake showed that the administration of liberal quantities of fat served to increase fat absorption and was associated with clinical benefit.

3. Emulsifying procedures failed to produce significantly better fat absorption.

4. The nature of the bone changes and the possible factors contributing to longevity in this condition are discussed.

REFERENCES

1. Niemann, A.: Ztschr. f. Kinderh. **4**: 152, 1912.
2. Koplik, H., and Crohn, B. B.: Am. J. Dis. Child. **5**: 36, 1913.
3. Ylppö, A.: Ztschr. f. Kinderh. **9**: 319, 1913.
4. Parker, W. S.: Am. J. Dis. Child. **5**: 386, 1913.
5. Hutchison, H. S., and Fleming, G. B.: Glasgow M. J. **94**: 65, 1920.
6. Freise, E.: Montaschr. f. Kinderh. **18**: 515, 1920.
7. Paul, S.: Ztschr. f. Kinderh. **34**: 216, 1922.
8. Wallgren, A.: Acta paediat. **6**: 123, 1926.
9. Moggi, D.: Riv. de clin. pediat. **32**: 257, 1934.
10. Wolff, J.: Arch. f. Kinderh. **121**: 125, 1940.
11. Chung, A. W.: J. PEDIAT. **33**: 1, 1948.
12. Chung, A. W., Morales, S., Snyderman, S. E., Lewis, J. M., and Holt, L. E., Jr.: Pediatrics **7**: 491, 1951.
13. Morales, S., Chung, A. W., Lewis, J. M., Messina, A., and Holt, L. E., Jr.: Pediatrics **6**: 86, 1950.
14. Rogers, C. S., Ferguson, C. C., Friedgood, E. H., and Vars, H. M.: Am. J. Physiol. **163**: 347, 1950.
15. Hoagland, C. L., Labby, D. H., Kunkel, H. G., and Shank, R. E.: Am. J. Pub. Health **36**: 1287, 1946.
16. Jones, C. M., Culver, P. J., Drummey, G. D., and Ryan, A. E.: Ann. Int. Med. **29**: 1, 1948.
17. Snyderman, S. E., Morales, S., and Holt, L. E., Jr.: To be published.
18. Park, E. A.: New York State J. Med. **24**: 921, 1924.
19. Gerstenberger, H. J.: Monatschr. f. Kinderh. **56**: 217, 1933.
20. Greaves, J. D., and Schmidt, C. L. A.: J. Biol. Chem. **102**: 101, 1933.
21. Heymann, W.: J. Biol. Chem. **122**: 249, 1937.
22. Thoenes, F., and Gruson, W.: Monatschr. f. Kinderh. **67**: 134, 1936.
23. Follis, R. H., Jr., Jackson, D. W., Eliot, M. M., and Park, E. A.: Am. J. Dis. Child. **66**: 1, 1943.
24. Park, E. A.: In Brennemann's Pediatrics (ed. by McQuarrie) vol. 1, Hagerstown, Md., 1951, W. B. Prior & Co., chap. 36, p. 83.
25. Stolkind, E.: Brit. J. Child. Dis. **36**: 115, 182, 295, 1939.
26. Ahrens, E. H., Jr., Harris, R. C., and MacMahon, H. E.: Pediatrics **8**: 628, 1951.

THE CAROTENEMIA OF HYPOTHYROIDISM

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AMONG the conditions responsible for carotenemia, hypothyroidism has occupied a prominent place. The regularity with which carotenemia occurs in this condition[1, 2, 3, 4, 5] as well as the observation that thyroidectomy in goats caused an increase in the carotene of the blood stream along with a reduction of vitamin A has led to the opinion that the carotenemia was specifically caused by lack of thyroid secretion.[6, 7] As a result of the observation on thyroidectomized goats, it was concluded that in the absence of the thyroid the animal lost the power to convert carotene to vitamin A with the result that carotene accumulated in the blood. The subsequent observation[2, 3, 4] that in human hypothyroidism the ratio of carotene to vitamin A in the blood is higher than in the normal individual strengthened this belief and led to its widespread acceptance as an adequate explanation of the facts. Most workers went even farther and concluded that the thyroid secretion specifically took part in the conversion, so that in its absence the conversion was impossible.

The possibility that thyroid secretion is in some way implicated in the conversion of carotene to vitamin A is an attractive one and at first sight seems to be justified by the facts. There is, however, one serious objection to the hypothesis as it stands. One may state it about as follows. For the conversion of carotene it is supposed that the carotene is removed from the blood stream and that the conversion takes place within the liver parenchyma by the action of a hypothetical enzyme, carotenase. From here on the hypothesis is vague but it seems to me that one of two things must happen—either the carotene not being utilized is regurgitated into the blood stream or the liver becomes saturated and no more is taken out of the blood stream. The latter possibility can be excluded by figures in the literature showing that in hypothyroidism there is no accumulation of carotene in the liver. The former possibility cannot be so easily excluded although on a priori grounds it seems unlikely.

The possibility that the carotenemia might be related to the high lipoid levels of hypothyroidism seems never to have been considered although even a superficial consideration of the literature showed that other conditions associated with lipemia were also associated with carotenemia, especially nephrosis, and, although to a lesser extent, diabetes. Moreover, there has never been a study of the effect on carotene levels of the administration and withdrawal of thyroid medication in cases of hypothyroidism. The work reported here is intended to provide such a study, with special attention to the hitherto neglected carotene-lipid relationship.

MATERIALS AND METHODS

The work to be reported was carried out on a number of hypothyroid in-

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dividuals. In all but one the hypothyroidism had been present from birth (cretins) or had developed in early life (juvenile myxedema). In one case the hypothyroid state had developed in an adult after total thyroidectomy. All the patients, except those on which single determinations were made, were under continual observation on a metabolism ward where their diets and activity were supervised. It has seemed unnecessary to prove the hypothyroid nature of the cases included here. They were, at the time, being studied by Wilkins and Fleischmann[8] and all conformed to the criteria advanced by these authors for the recognition of hypothyroidism.

The methods used for the determination of carotene and total lipids have been given in some detail in a previous communication.[9] Serum for the determination was obtained by venepuncture, usually after an overnight fast, but occasionally four to five hours after a meal. It was found that these differences in obtaining the blood were of little importance.

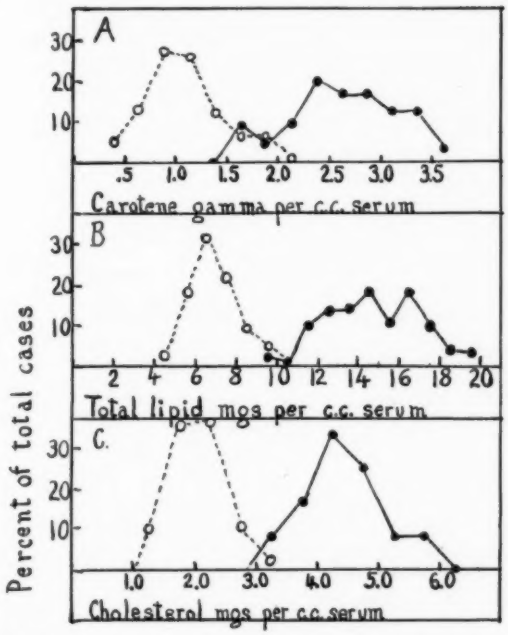

Chart 1.—Curves showing distribution of serum levels of carotene, total lipid, and cholesterol in normal and hypothyroid individuals. Note: The broken lines represent the figures for the normal individuals; the continuous lines, those for the hypothyroid.

RESULTS

The carotenemia of hypothyroidism is demonstrated in Chart 1, *A*, in the form of a distribution curve compared with a similarly constructed curve for the carotene of normal individuals. The normal curve was based on figures from forty well-nourished healthy children above the age of 4 years. The hypothyroid curve was based on twenty-five observations made on six-

teen hypothyroid children, most of them examples of cretinism, who had been off thyroid medication for a sufficient time to permit stabilization of figures, a matter of six weeks more or less. When two observations were made on the same patient the second was made at least six months after the first, following a period of adequate treatment and a second withdrawal.

It is readily appreciated that nearly all the hypothyroid figures lie above the highest of the normal figures. It must of course be recognized that since carotene of the blood is largely dependent on the ingested carotene, it was necessary to select cases that were comparable from a dietary standpoint, and therefore to exclude normal children with carotenemia from excessive ingestion as well as cretins in the first year of life who were not receiving foods that contained carotene.

Chart 1, *B* and *C* contain similar distribution curves for total lipid and cholesterol, respectively, the figures obtained from the same blood samples used for the determination of carotene. The separation of the normal and hypothyroid curves is evident. There is, of course, nothing new in this demonstration, but it is well to emphasize that total serum lipid levels could just as well be used in the diagnosis of hypothyroidism as the serum cholesterol levels. Radwin, Michelson, Melnick, and Gottfried[10] even claim that serum lipid levels are a better indicator of hypothyroidism than the cholesterol levels.

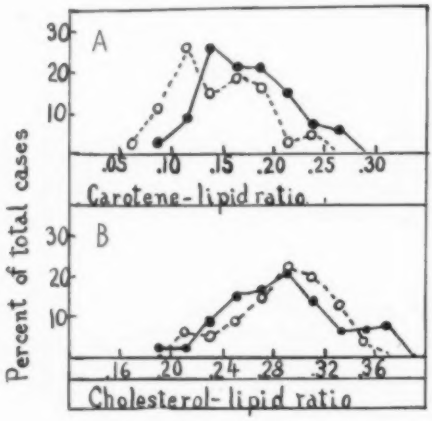

Chart 2.

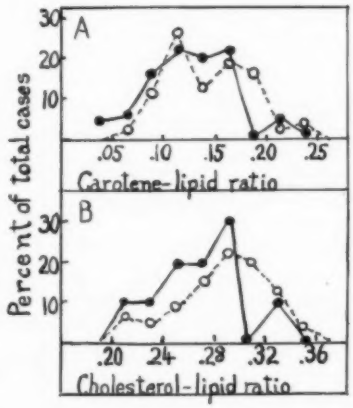

Chart 3.

Chart 2.—Curves showing the distribution of serum carotene-lipid ratios and cholesterol-lipid ratios in normal and hypothyroid individuals.

Chart 3.—Curves showing the distribution of serum carotene-lipid and cholesterol-lipid ratios in normal and treated hypothyroid individuals.

Chart 2, *A* represents the carotene lipid ratio of hypothyroidism compared with the normal, while Chart 2, *B* represents the cholesterol-lipid ratio in hypothyroid and normal cases. It is quite evident that in the case of the cholesterol-lipid ratios the two curves have just about the same shape and range. In the case of the carotene-lipid ratios, on the other hand, the distribution of values in hypothyroid-

ism covers a somewhat higher range than in the normal.

The tendency to a slightly higher carotene-lipid ratio in hypothyroidism not shared by the cholesterol-lipid ratio appears to be important since it indicates the presence of some factor connected with the hypothyroidism which has a special influence on the serum carotene levels leading to an accumulation greater than that of the lipids and cholesterol. The nature of this factor will be discussed later.

Chart 3 shows the effect of administration of thyroid extract on the carotene-lipid and cholesterol-lipid ratios. It is obvious that the distribution of values in the treated hypothyroid cases and the normal are identical.

EFFECT OF TREATMENT AND ITS WITHDRAWAL

All the figures thus far discussed were obtained after treatment or its withdrawal had been continued for a period sufficient to insure stabilization. The next group of charts represents the course of the carotene and lipid levels following administration or withdrawal of thyroid medication. In

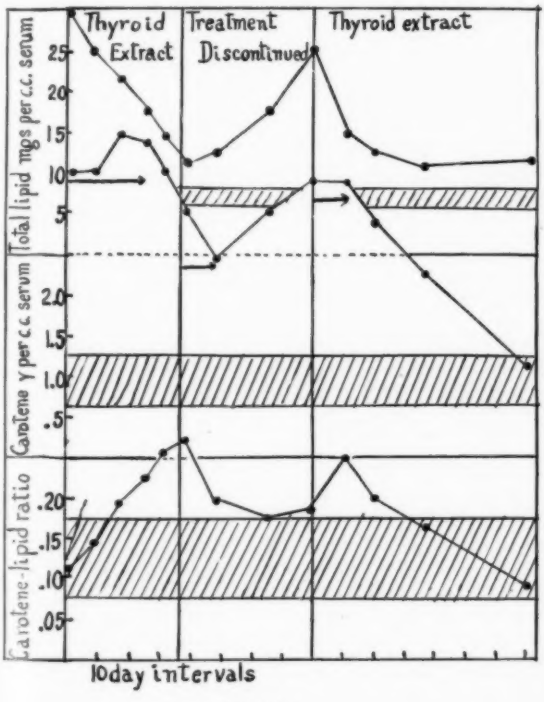

Chart 4.

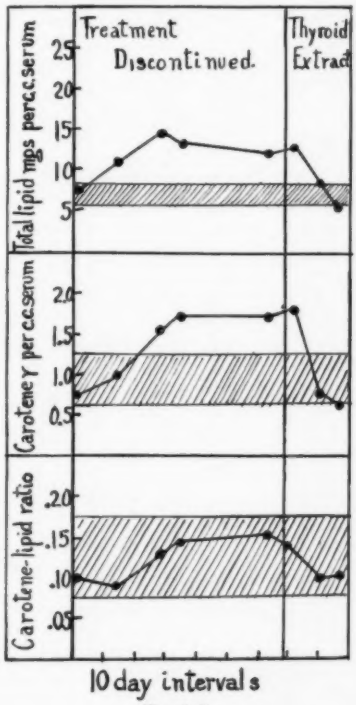

Chart 5.

Chart 4.—The effect of treatment (thyroid extract) and its withdrawal on the total lipid, carotene, and carotene-lipid ratios in an adult hypothyroid individual (postoperative). Note: The shaded areas represent the range of the values found in normal individuals. The horizontal arrows represent the periods in which the carotene level lags behind the lipid level in its response to treatment or withdrawal of treatment.

Chart 5.—Course of serum lipid, carotene, and carotene-lipid ratio in a treated cretin on withdrawal and reinstitution of treatment.

spite of considerable individual variation in response certain generalizations may be made. The charts do not represent all the material but have been chosen for purposes of illustration.

1. Total lipid. The rise of lipids on withdrawal of treatment took place promptly and continued to a point well above the normal, stabilization at the higher level being accomplished in about four to six weeks (Charts 4, 5, 6, 7). While the level representing the new equilibrium varied considerably from individual to individual, it was relatively constant in any single case. The fall in lipid level after institution of treatment with thyroid extract was likewise prompt.

2. Carotene. The rise and fall of the carotene levels followed the rise and fall of the lipid levels with considerable fidelity. Moreover, in general, the higher lipid levels were associated with higher carotene levels and the lower lipid levels with lower carotene levels. The carotene response, however, was not always as prompt as the lipid response. The lag in carotene is responsible for a number of apparent discrepancies in the behavior of carotene.

3. Lag in carotene. This is clearly seen in Chart 4 in which there was a

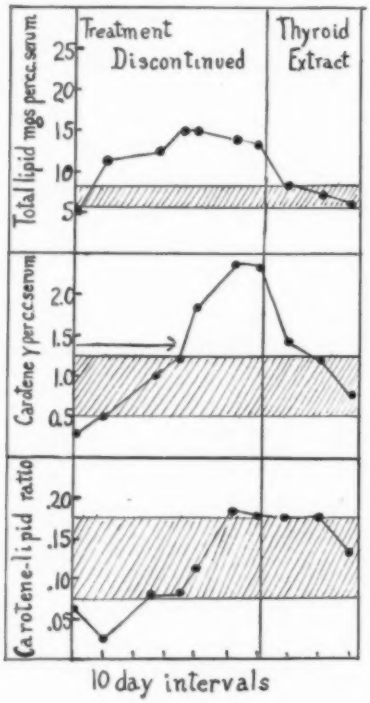

Chart 6.

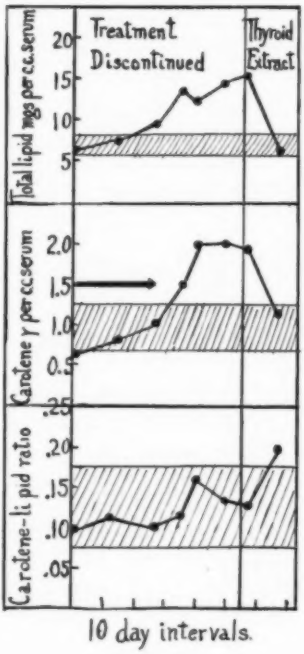

Chart 7.

Chart 6.—Course of serum lipid, carotene, and carotene-lipid ratio in a treated cretin on withdrawal and reinstitution of treatment.

Chart 7.—Course of serum lipid, carotene, and carotene-lipid ratio in a treated cretin on withdrawal and reinstitution of treatment.

lag of three weeks more or less in the response of carotene to the initial treatment, followed later by a lag of a week in response to withdrawal, and again by a lag of a week on reinstitution of treatment. The carotene lag is also clearly seen in Chart 8 on institution of treatment. In other cases was allowed for the observation. The lag in carotene response was, however, responsible for an apparent paradoxical result when time was not allowed for eventual stabilization. These consist of initial rises in the ratio when treatment was instituted and initial falls when treatment was discontinued.

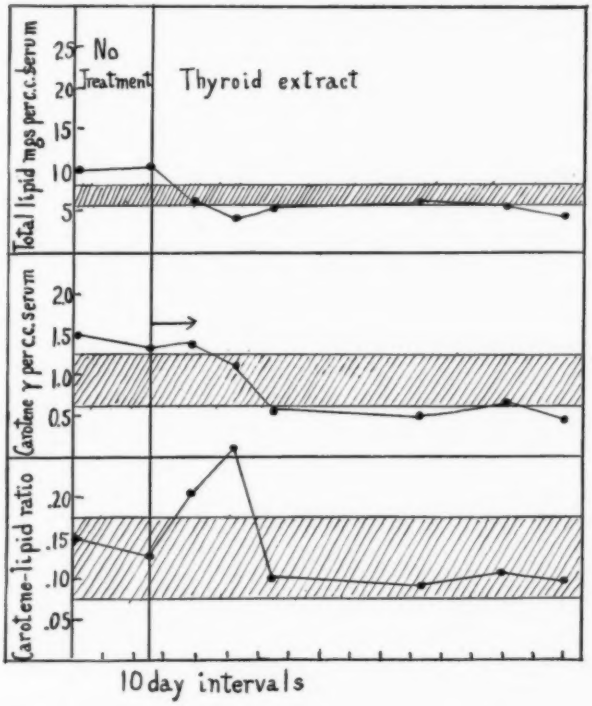

Chart 8.—Effect of treatment with thyroid extract on the serum lipid and carotene in a mild hypothyroid individual.

as in Charts 6 and 7 there was a rather slow initial rise when treatment was discontinued followed later by a more rapid rise. In general, the lag was more likely to be present when treatment was discontinued than when treatment was instituted.

4. Carotene-lipid ratios. These, in general, rose when treatment was discontinued and fell when treatment was instituted, provided a sufficient time

The behavior of carotene may be simply summarized:

1. Carotene levels are closely correlated with lipid levels.

2. Changes in carotene level often lag behind those of the lipids sometimes to a considerable degree.

3. Carotene tends to accumulate in the blood to a greater degree than the total lipids during hypothyroid periods (high carotene-lipid ratio).

DISCUSSION

The tendency of carotene to accumulate in the blood to a greater extent than the other lipids seems to indicate the presence of some factor associated with hypothyroidism that affects the carotene but not the other lipids. Before we can attempt to explain the accumulation of carotene in the blood, it will be necessary to review briefly what we know of carotene blood levels.[11]

1. The carotene of the blood is derived almost exclusively from the carotene being ingested. When ingested in excessive amounts, its level in the blood rises; when eliminated from the diet, its level falls, and in a relatively short time carotene is absent from the blood stream. There is apparently no recognizable tendency for the body to "regulate" the level of carotene.

2. The "stores" of carotene contained in the fat depots of the body are unavailable for maintaining a recognizable amount in the blood. Even during starvation when fat stores are being broken down, carotene is not freed in appreciable amounts.

3. Carotene is closely dependent on the lipids which apparently serve as a vehicle not only for storage, but also for absorption from the intestines and probably for transport in the blood stream. In conditions that interfere with digestion or absorption of fat, carotene is absent from the blood. High fat diets promote the absorption of carotene. Moreover, the rate at which carotene rises in the blood stream during ingestion of test doses can be correlated with the level of total lipid in the blood.

4. Movements of carotene in the body are sluggish compared with other lipids and especially with vitamin A. Examples of "sluggishness" of carotene response have been given above, but there are also others. Absorption curves of vitamin A and of lipids in general are measured in hours, those of carotene in days. In pneumonia, serum vitamin A may be reduced to traces and other lipids to low figures in two to three days, while reduction of carotene is a matter of a week or more.[12]

5. In general, carotene behaves as an inert substance dependent on the lipids for its movements in the body and having no effect upon the body's economy except as a precursor of vitamin A. However, excessive ingestion may in some cases be followed by certain toxic effects, which are similar to those arising from excessive vitamin A ingestion, but are due to carotene and not to vitamin A.

6. Carotene enters the liver through ingestion by reticuloendothelial cells from which it passes on to the liver cells. Whether there is any equilibrium between the concentration in the liver and that in the blood stream is not known. There is no such equilibrium in the case of vitamin A and presumably there would be none in the case of carotene.

As was indicated above, the level of carotene in the blood stream depends on its absorption from the intestinal tract. When this is relatively low as is the case when the lipid levels of the blood are normal or low, the blood level will lie within a certain range usually considered normal. Of course, this level will depend somewhat on ingestion but the rate of removal will ordinarily balance the rate of entrance, so that within a fairly wide range of ingestion the blood level will tend to

be constant. This statement holds true for hypothyroidism in which adequate treatment with thyroid extract is being maintained. When thyroid medication is discontinued, the lipid levels rise but the relatively slow absorption of carotene may cause the rise in its level to lag behind that of the lipids. Then as the higher lipid levels exert their accelerating influence on carotene absorption, the plasma carotene rises to a point commensurate with the plasma lipids. However, the high lipid levels have also a second effect, namely, that of holding the carotene in solution in the plasma so that accumulation takes place and the carotene-lipid ratio rises to the higher levels characteristic of the hypothyroid state.

When thyroid medication is instituted, the relatively slow removal of carotene from the blood may serve for a time to delay a fall in carotene commensurate with the fall in lipids, so that there may be an initial rise in the carotene-lipid ratio.

It has been assumed that because there is failure to convert carotene to vitamin A in hypothyroidism, thyroxin is essential to the conversion. The observations reported here suggest that the carotene-lipid relationship may also be a factor in the failure of the conversion.

SUMMARY

Twenty-five cases of hypothyroidism were studied from the point of view of carotenemia, a number of them over a period of time during which thyroid medication was withdrawn and reinstituted.

The occurrence of carotenemia in hypothyroidism, long known, is confirmed. However, it is found only in those who ingest food containing carotene, so is not likely to be encountered in infancy.

It is regularly associated with lipemia and cholesterolemia, but the carotene tends to be relatively more increased than the lipids or cholesterol.

It was also found that when thyroid medication was withdrawn or instituted the resultant rise or fall in carotene tended to lag behind that of the total lipid. It was pointed out that carotene was probably "carried" by the lipids and as a result would not only show some lag in movement but would tend to accumulate in the blood stream when the lipids were increased.

It was felt that this behavior of carotene might well be a factor in the "failure" to convert carotene to vitamin A in hypothyroidism.

REFERENCES

1. Umber, F.: Klin. Wchnschr. **53**: 829, 1916.
2. Wendt, H.: München. med. Wchnschr. **82**: 1679, 1935.
3. Wendt, H.: Deutsches med. Wchnschr. **62**: 1213, 1936.
4. Clausen, S. W., and McCoord, A. B.: J. PEDIAT. **13**: 635, 1938.
5. Lindqvist, T.: Acta med. scandinav. suppl. **97**: 1938.
6. Fasold, H., and Heidemann: Ztschr. Exper. Med. **92**: 53, 1934.
7. Schneider, E., and Widman, E.: Klin. Wchnschr. **14**: 786, 1935.
8. Wilkins, L., and Fleischmann, W.: J. A. M. A. **116**: 2459, 1941.
9. Josephs, H. W.: Bull. Johns Hopkins Hosp. **65**: 112, 1939.
10. Radwin, L. S., Michelson, J. P., Melnick, J., and Gottfried, S.: Am. J. Dis. Child. **60**: 1120, 1940.
11. The evidence for what follows was reviewed in Josephs, H. W.: Am. J. Dis. Child. **67**: 33, 1944.
12. Josephs, H. W.: Am. J. Dis. Child. **65**: 712, 1943.
13. Drill and Truant: Endocrinology **40**: 259, 1947.

THE TREATMENT OF THE NONEDEMATOUS NEPHROTIC CHILD WITH ACTH

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BROOKLYN, N. Y.

LIPOID nephrosis occupies a position shared by few diseases in medicine—its etiology is unknown, its course unpredictable, its prognosis uncertain, and its treatment unsatisfactory. Nevertheless, its cardinal manifestations, edema, hypoproteinemia, albuminuria, hypercholesterolemia, and hyperlipemia are so striking and the remissions or exacerbations at times so dramatic as to challenge the attention of both the clinician and the scientist.

Treatment has been directed toward the elimination of edema while its less obvious manifestations have been left to take their natural course. Although other agents and procedures have been found to provoke diuresis, with none of these have the results been as consistent as with ACTH. All observers agree that diuresis can be induced in over 70 per cent of the cases of uncomplicated lipoid nephrosis after one or more courses of treatment.[1, 2, 3, 4] While this does not result in cure, except in a small percentage of cases, certain phenomena have been noted to follow either before, during, or after diuresis: (a) a decrease in proteinuria[3, 4, 5, 6]; (b) a decrease in the physical elements in the urine[4]; (c) an increase in the serum albumin concentration and to a lesser degree in the plasma protein[3, 4, 5, 6]; (d) a restoration of the normal electrophoretic pattern of the blood with the exception of the gamma globulin which remains low[7, 8]; (e) a drop in the hypercholesterolemia and the hyperlipemia[3, 4, 5, 7]; (f) a reduction in the erythrocyte sedimentation rate (E.S.R.), sometimes to a normal level[5]; (g) an increase of the diminished plasma complement concentration[8]; (h) a reduction in the blood concentration of the antidiuretic hormone of the neurohypophysis[6]; (i) an increase of the glomerular filtration rate to normal or to supernormal levels with less striking and less uniform improvement in the effective renal plasma flow and in tubular function[9]; (j) a reduction of the abnormal sodium-retaining activity of urinary corticoids[4]; (k) a restoration of the normal capacity of the renal tubules to reject sodium.[10]

Some of these results have been the subject of a previous communication from this department[5] and for the most part have confirmed the observations of other workers. In this paper we are (1) presenting additional data on a larger series of cases, (2) presenting our results in the treatment of the nonedematous ne-

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phrotic child, i.e., one who has already diuresed, with ACTH.

In reviewing our first series of twelve cases treated with ACTH it was found that recurrence of edema in a few weeks or months was the rule. Of eleven patients who had a diuresis all but one had recurrence of edema within ten weeks. Several were retreated, but in every case edema recurred in less than two months. At present three of these patients have had prolonged remissions and are perhaps cured, but the course of the disease in this group has not been very different from that of similar groups observed prior to the introduction of ACTH therapy.

Moreover, it was noted in this series that treatment with ACTH was followed by changes in the serum proteins, lipids, the sedimentation rate, and in albuminuria. These changes were all in the direction of normality. In all of the cases one or more of these changes were detected before diuresis. In every case a decrease in albuminuria was detected. Though these changes were in the direction of normality, only in the case of the sedimentation rate were normal values obtained with any degree of frequency. With return of edema all these values were found to return to their previous levels. Since these changes begin before diuresis, they would seem to be primarily the result of ACTH administration rather than of diuresis itself. An attempt was made to determine whether it was possible to further alter these values in the direction of normality by the administration of ACTH *following* diuresis and to determine what effect this would have on the course of the disease.

Thus far we have treated eight patients in this manner. The age of the patients varied from 21 months to 5 years. None of these patients was found to have persistent azotemia, hypertension, or gross hematuria during the period that they were being observed.

The procedure followed was to administer ACTH for ten to seventeen days. Diuresis either began while the drug was being administered or shortly after it was discontinued. After a period of one to two weeks, a second "course" of ACTH was begun and the drug given for another ten to seventeen days. The dosage used was 25 mg. every six hours except where previous experience indicated that a larger dose would probably be necessary or when hypertension developed and it was necessary to decrease the dose. This pattern of two "courses" was chosen arbitrarily, as it was felt that a one- to two-week rest might lessen the incidence of complications. All patients were placed on prophylactic antibiotics and oral potassium chloride. Routine urine analyses were performed daily. Blood was taken two or three times per week and analyzed for the following:

Erythrocyte sedimentation rate	—Westergren method.
Total and free cholesterol	—Colorimetrically by the method of Kaye.[11]
Total protein	—Micro-modification of the biuret method of Kingsley.[12]
Albumin	—Sodium sulfite biuret method.[13]
Sodium and potassium	—Flame photometer.
Urea	—Sobel, Hirschman, and Besman.[14]
Fibrinogen	—Salting out followed by biuret method.
Total lipid	—Extraction with chloroform.

It will probably be most convenient to present our results at three levels: the clinical, the laboratory, and the "follow-up."

A. *Clinical.*—Clinically there was a striking uniformity in result. All of our eight patients had a diuresis with their first course beginning usually developed an increased appetite which in some instances was marked. All patients gained weight during this second course, in one instance as much as 12 pounds over a seventeen-day period and all developed the protuberant abdomen and moon face seen with prolonged ACTH therapy.

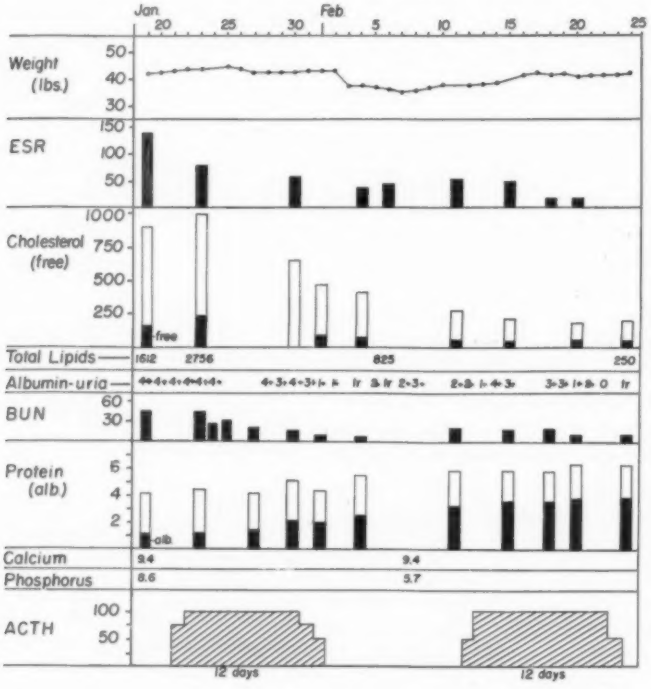

Chart 1.

while the ACTH was being administered and continuing after its cessation until all patients were clinically edema-free. The average weight loss was 9.6 pounds. Those patients who had voluntarily confined themselves to bed while edematous became ambulatory and playful following diuresis.

When, after a week or two, the second course was begun, the patients

When ACTH was discontinued, these effects disappeared in a few days and there was a loss of weight. However, there remained a net increase of weight above that which obtained when the second course was begun, this despite the fact that all patients remained clinically edema-free. Apparently the large quantities of food consumed resulted in an in-

crease of true weight and this was reflected in the physical appearance of the children.

B. *Laboratory.*—The chemical data are summarized in the accompanying charts. Charts 1, 2, and 3 show the changes in individual representative cases while Table I gives the average change. It will be noted that there is

Gm. per cent at the completion of the second course to 3.1 Gm. per cent one month later. Excluding this patient the average serum albumin one to two months later would be 4.24 Gm. per cent, a very striking figure. The total protein did not rise as much as the albumin which is accounted for by a slight drop in serum globulin. There

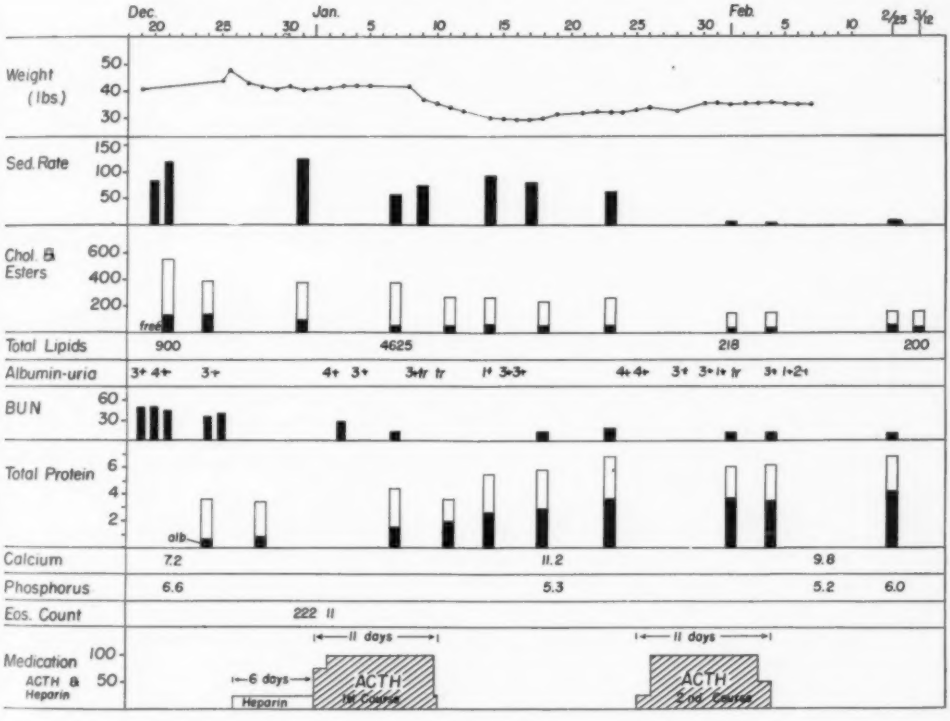

Chart 2.

a gradual and continuous rise of the serum albumin which takes place while ACTH is being administered and this rise continues after the drug is discontinued, both after the first and second courses. All patients, with one exception, showed this progressive pattern. In this patient the serum albumin fell from a level of 3.7

is a gradual and steady fall of the serum lipids and the cholesterol fraction while the cholesterol esterification remained fairly constant. It should be noted that all values listed in the final column are within normal limits. With one exception there was a sharp drop in albuminuria preceding diuresis. When heavy albumi-

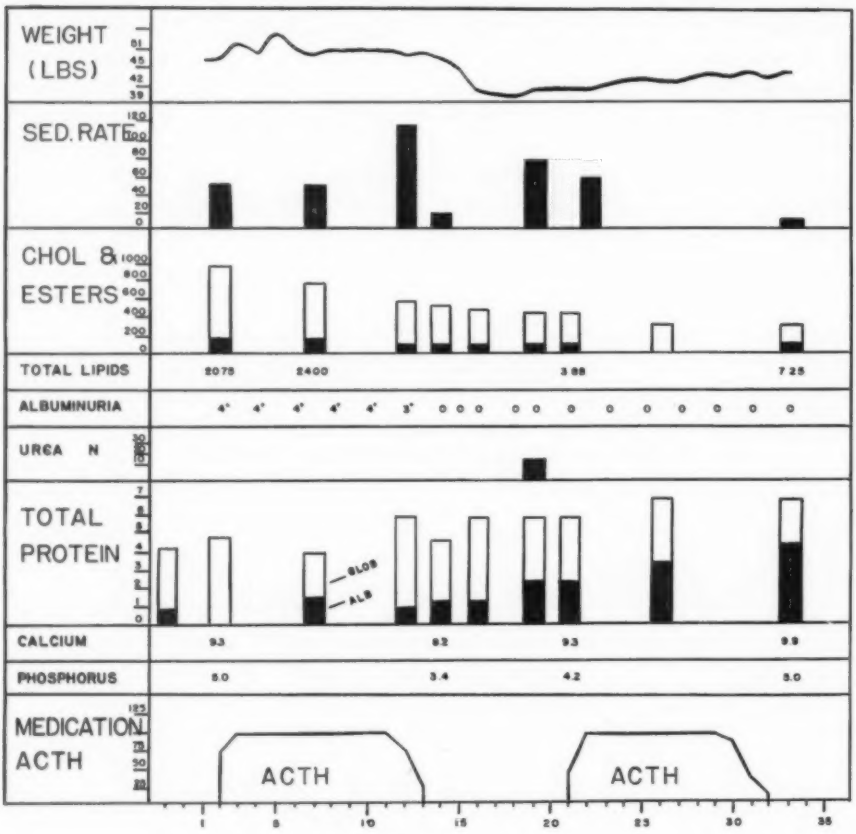

Chart 3.

TABLE I. AVERAGE VALUE OF EIGHT PATIENTS TREATED WITH TWO COURSES OF ACTH

	PRE-TREATMENT	END OF FIRST COURSE	BEGINNING OF SECOND COURSE	END OF SECOND COURSE	1-2 MONTHS LATER†
Serum albumin Gm. %	1.39	2.10	2.61	3.80	4.05
Serum globulin Gm. %	2.69	2.47	2.69	2.27	2.40
Total protein Gm. %	4.09	4.87	5.30	6.07	6.45
Total lipid mg. %*	1,770	1,039	–	602	–
Total cholesterol mg. %	659	435	357	238	234
Percentage cholesterol esterified	36.8	39.6	40.5	35.6	39.6

*Based on determination on four patients.

†Based on determination on six patients. Average value of these six at end of second course was: albumin, 3.84; globulin, 2.33; cholesterol, 264; per cent esterified, 39.4.

nuria recurred after ACTH was discontinued, it tended to diminish during the second course. The sedimentation rates, which were markedly elevated in all cases (50 to 130 mm.), returned to normal in six cases. The initial fibrinogen levels were elevated normal following the second course, and in one patient a normal value was not obtained. Three patients had an elevated blood urea nitrogen (40 to 66 mg. per cent) and in all three this value fell to normal during the first course.

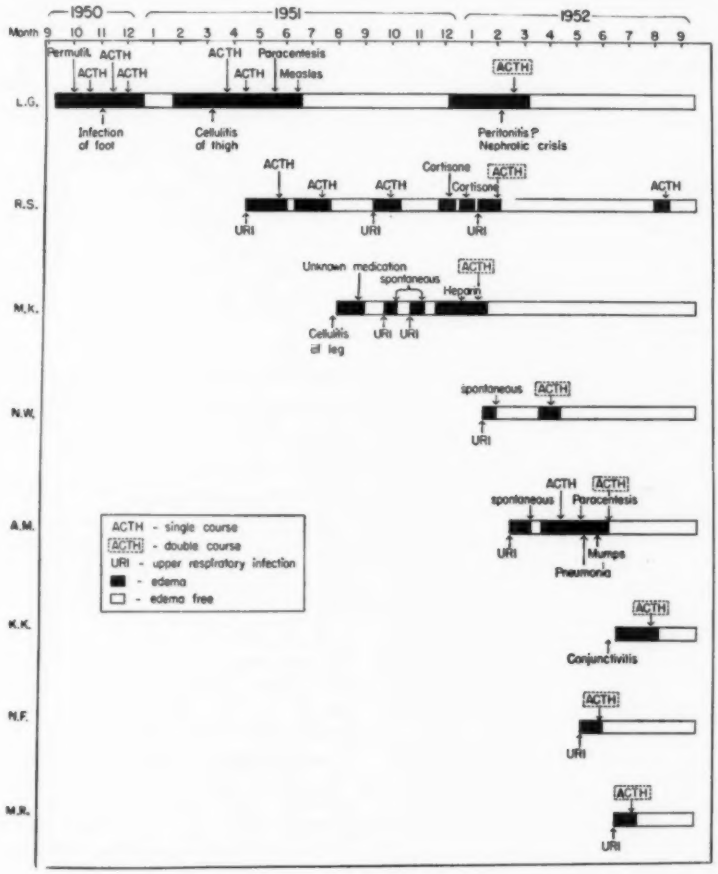

Chart 4.—Follow-up of eight patients treated with double courses of ACTH.

in the seven patients in whom this value was obtained (0.6 to 1.1 Gm. per cent). In three cases this value became normal after the first course. In three others this value returned to

C. *"Follow-up."*—Chart 4 illustrates the effects on the course of the disease. These patients have now been followed from one and one-half to eight months since discharge. Only

one patient has relapsed after being edema-free for five and one-half months.

Patient L. G. has had nephrosis for two years. He was unsuccessfully treated with Permutit and then given three courses of ACTH in succession. During each of the first two courses he was given 60 mg. a day for ten days with no change in the blood chemical pattern and no diuresis. During his third course he received 100 mg. of ACTH a day for seventeen days, after which he diuresed and lost 30 pounds with improvement of his blood chemical pattern. One month later edema again became evident and he was given two further courses of ACTH, 100 mg. a day for ten days, and 100 mg. a day for nine days, with no effect. He was then exposed to measles and diuresed. Five and one-half months later edema recurred and he developed a nephrotic crisis (peritonitis?). He responded to antibiotics and was then given 100 to 125 mg. of ACTH a day for seventeen days which was followed by diuresis and a weight loss of 17 pounds. A second course of 100 to 140 mg. a day for seventeen days produced a weight gain of 12 pounds. He has remained well and edema-free for over six months. He continues to show 4+ albuminuria and his chemical pattern remains slightly abnormal—albumin 3.7 Gm. per cent, cholesterol 300 mg. per cent, blood urea nitrogen 18 mg. per cent.

R. S. was treated successfully with five different courses of ACTH or cortisone prior to her "double course." Her remissions lasted from a few days to almost two months. The laboratory data are summarized in Chart 1. After a "double course" she remained edema-free for five and one-half months and then relapsed. Four months following the "double course" her albumin had fallen to 3.1 Gm. per cent. Her cholesterol had risen to 359 mg. per cent. When edema recurred her albumin was 1.2 Gm. per cent, cholesterol 660 mg. per cent.

M. K. has had nephrosis for over a year. She was treated at another hospital with an oral medication which resulted in temporary remission. Two upper respiratory infections were followed by exacerbations and spontaneous diureses. During the third episode of edema she developed pneumonia. The pneumonia was treated successfully and the patient then given a "double course." The chemical data can be found in Chart 2. She has been completely well for eight months now. Her chemical pattern has been repeatedly tested and has remained normal. Latest result: albumin 4.2 mg. per cent, cholesterol 175 mg. per cent, blood urea nitrogen 17 mg. per cent. Her urines show an albumin-free urine to 1+ albuminuria.

H. W. has remained completely well for five months following treatment. Her chemical pattern has remained normal. Latest result: albumin 4.3 Gm. per cent, cholesterol 234 mg. per cent, erythrocyte sedimentation rate 10 mm., blood urea nitrogen 14 mg. per cent. Her urines contain from none to 1+ albumin. The chemical data can be found in Chart 3.

A. M. was given ACTH which was discontinued after ten days when he developed pneumonia. Diuresis did not occur at this time but he later developed mumps which was followed by a partial diuresis. Since his "double course" of ACTH he has remained clinically well for three months with an abnormal chemical pattern. Latest result: albumin 3.1 Gm. per cent, cholesterol 300 mg. per cent, erythrocyte sedimentation rate 30 mm., blood urea nitrogen 11 mg. per cent. Urines show 2 to 3+ albumin.

K. K. has remained well for one and one-half months with a normal chemical pattern. Albumin 4.4 Gm.

per cent, cholesterol 224, erythrocyte sedimentation rate 15 mm., blood urea nitrogen 14 mg. per cent. Urines show a trace to 1+ albumin.

N. F. has remained well for three and one-half months with no albuminuria and a normal chemical pattern. Albumin 4.6 Gm. per cent, cholesterol 219 mg. per cent.

M. R. has remained well for two and one-half months. His urines contain a trace of albumin, but no chemical data are available.

Note: Since Chart 4 was prepared, two patients, N. W., and A. M., have had a return of edema after five and one-half and three months, respectively.

COMPLICATIONS

The complications seen are the same as those observed with single courses of ACTH. Hypertension, when it occurs, necessitates a reduction of dosage. Hyperglycemia and glycosuria are rare and at no time has it been necessary to discontinue therapy because of these phenomena. Hypokalemia has been noted six times out of a total of forty-two courses, with serum potassium levels varying from 2½ to 3 meq. per liter. In every case hypokalemia was observed at the time of diuresis. Generous doses of oral potassium chloride rapidly restore the serum potassium to normal. We have seen hypokalemia even with prophylactic oral potassium chloride, and there is as yet no evidence to indicate whether prophylactic therapy is of any value. Infections have occurred even when prophylactically antibiotics were used.

Thus far there have been three deaths among the twenty patients treated with ACTH. One patient died at another hospital after several months of hypertension and increasing azotemia. Two patients have died during ACTH therapy—the first death occurred in a patient who showed anemia, azotemia, and hypertension prior to therapy. A course of ACTH resulted in diuresis and a fall of the blood urea nitrogen from 80 to 30 mg. per cent. Hypertension continued, however, and two days after a second course was begun the patient expired in pulmonary edema. Autopsy showed chronic glomerulonephritis, a large heart, and pulmonary edema. In retrospect, this patient doubtless should *not* have received ACTH as persistent hypertension was present. The second death occurred in the only patient that we have treated with a long-acting ACTH preparation (Acthar Gel, Armour). This patient convulsed on the ninth day of therapy during the height of diuresis and expired. Autopsy was refused and we have no explanation for this death. Blood taken at the time of death was analyzed for serum calcium, sodium, potassium, chloride, and CO_2 content, and essentially normal results were obtained.

DOSAGE

The dosage of ACTH recommended for the therapy of the nephrotic child varies considerably. It has been stated that 50 mg. of ACTH per day produces diuresis with as much regularity as larger doses.[15] Another group calculates dosage on the basis of surface area, 150 to 200 mg. per day per square meter of body surface.[16]

We have been using ACTH in treating nephrosis for two years. During the first year the doses used varied considerably as we had not yet developed a standard procedure. Eighteen courses of ACTH were given to eleven patients with twelve successful results. Table II presents these results analyzed on the basis of dose per square meter per day. (Surface area calculated on basis of dry weight.)

It will be noted that above 150 mg. per day per square meter all patients had a complete diuresis. Between 101 and 150, five out of eight patients had a complete diuresis. Below 100 only one out of five had a complete diuresis. Particularly interesting is one patient who was treated five times during the year (L. G.), with only one successful result. Diuresis occurred when 135 mg. per day per square meter was given for seventeen days, but the same dose given for nine and ten days on two different occasions had no effect, nor did smaller doses given two other times. This patient has subsequently been treated with 167 mg. per day per square meter for seventeen days with complete diuresis.

During the second year we have been using larger doses, usually 100 mg. per day, but sometimes more with children more than 4 years of age. In every case the dose used has exceeded 150 mg. per day per square meter. Twelve courses of ACTH have been given during this second year in an attempt to promote diuresis, and in only one instance was complete diuresis not obtained—this in a patient who developed pneumonia during treatment. Thus the incidence of complete diuresis using more than 150 mg. per square meter of body surface per day is sixteen out of seventeen trials or 94 per cent.

TABLE II

	MG. ACTH PER DAY PER SQUARE METER	% OF WEIGHT LOST (ON BASIS OF EDEMA WEIGHT)	RESULT
R. S.	352	12	Complete diuresis
D. H.	190	31	Complete diuresis
R. S.	180	19	Complete diuresis
W. H.	166	26	Complete diuresis
J. H.	154	29	Complete diuresis
L. G.	135	42	Complete diuresis
L. G.	135	3	No diuresis
L. G.	135	0	No diuresis
I. G.	129	22	Complete diuresis
M. S.	120	25	Complete diuresis
M. S.	120	37	Complete diuresis
H. M.	109	23	Complete diuresis
M. B.	104	5	Partial diuresis
W. H.	100	18	Complete diuresis
H. G.	100	7	Partial diuresis
L. Ce. G.	86	6	Partial diuresis
L. G.	81	2	No diuresis
L. G.	79	0	No diuresis

DISCUSSION

Many observations are available which can be utilized to elucidate the mechanism of the ACTH-induced diuresis. Approaching the problem as

primarily a renal one, the increase in glomerular filtration rate and renal blood flow, the decrease in the avidity of the distal tubule for sodium, the depression of the blood antidiuretic hormone level, and the depression of the salt-retaining corticoid activity are all mechanisms that help to explain why the kidney suddenly begins to excrete large quantities of sodium chloride and water. On the other hand, the diminution in the amount of protein lost in the urine which has been noted to precede diuresis and the observation that ACTH can elevate the serum albumin in disorders in which proteinuria is not present (portal cirrhosis,[17] rheumatic fever[18]) helps to explain the elevation of serum protein and the consequent rise in serum oncotic pressure that withdraws fluid from the intercellular spaces.

It is thus clear that many mechanisms have been uncovered which can afford plausible explanations for diuresis. Several of these require further confirmation. What is not known is the relative importance of each of these mechanisms, and just how they are interrelated so far as cause-effect relationship and time sequence are concerned. For example, the reduction of the blood antidiuretic hormone level may represent a response of the posterior pituitary to the increased blood volume preceding diuresis. And, again, the relative importance of diminished proteinuria as compared to increased synthesis of protein in producing the observed increase in serum protein is not yet clear. Other examples can be given, but too much cannot be gained from such speculation at present. It is unlikely that a simple explanation for the entire mechanism of diuresis will be forthcoming, but enough data have been accumulated to indicate the direction in which further investigation is likely to prove most rewarding.

ACTH does more than induce diuresis, however. When administered to patients following diuresis there is a continued improvement of the abnormal chemical pattern until in most instances a normal one can be obtained. This is important for several reasons: (1) It makes possible a study of the mechanism which determines the level of these components in the plasma. It can be guessed that whatever the mechanism is that is concerned in this process it is one that simultaneously affects all these components, that is, plasma proteins and lipids, for as one component is rising the other is falling in what appears to be a very definite manner that speaks for a common point of contact in intermediary metabolism. There is also the fact to be considered that in disorders such as starvation hypoproteinemia, the lipids are not elevated, but reduced, while in diabetes mellitus and gout there may be hypercholesterolemia without hypoproteinemia. (2) It appears that by restoring the chemical pattern to normal a longer period of clinical remission ensues. In our initial series of patients treated with single courses of ACTH those patients who diuresed left the hospital with an average serum albumin of 3.1 Gm. and an average serum cholesterol of 573 mg. per cent. Ten out of eleven of these patients enjoyed a remission of less than ten weeks' duration. In the

present series all but one patient have been followed for longer than ten weeks and no patient has relapsed before this time, and there are two patients in our present series who previously had much shorter remissions with single courses of ACTH than they are enjoying or have enjoyed after a double course. The exact value of this method of administering ACTH must await further experience. The method here described does have the disadvantage of requiring more prolonged hospitalization with increased expense to the family and possibly more psychiatric trauma to the child. This has to be weighed against the longer period of clinical remission that seems to ensue, and the fact that serious infections requiring hospitalization are not likely in the nonedematous nephrotic child.

CONCLUSIONS

1. ACTH administered to the nonedematous nephrotic child, that is, one who has recently diuresed as a result of ACTH therapy, produces striking improvement of the abnormal blood chemical pattern seen in this disease. In many cases a normal pattern is obtained.

2. Treatment of a nephrotic child in the above manner seems to prolong the period of remission usually seen when ACTH is given merely to obtain diuresis. The exact length of prolongation must await further experience.

3. The dosage of ACTH used to obtain diuresis should vary with the size of the child. Between 150 and 200 mg. per day per square meter should be administered for about ten days. For convenience in children under 5 years of age, this dosage can be approximated by using the figure 3 to 4 mg. per day per pound of dry weight.

4. The mechanism of action of ACTH is discussed.

REFERENCES

1. Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Roche, M., Staehelin, D., and Wilson, D. L.: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242:** 824, 1950.
2. Riley, C. M.: Nephrotic Syndrome: Effect of Adrenocorticotrophic Hormone, Pediatrics **7:** 457, 1951.
3. Rapoport, M., McCrory, W. W., Barbero, G., Barnett, H. L., Forman, C. W., and McNamara, H.: Effect of Corticotropin (ACTH) on Children With the Nephrotic Syndrome, J. A. M. A. **177:** 1101, 1951.
4. Luetscher, J. A., Jr., Deming, O. B., and Johnson, B. B.: A Comparison of Effects of ACTH and Cortisone in Nephrosis, J. Clin. Investigation **30:** 658, 1951.
5. Kramer, B., Casden, D. D., Goldman, H., and Silverman, S. H.: Effect of the Adrenocorticotrophic Hormone on Nephrosis in Childhood, Postgraduate Med. **11:** 439, 1952.
6. Lauson, H. D., Forman, C. W., McNamara, H., Mattar, G., and Barnett, H. L.: The Effect of ACTH on Glomerular Permeability to Albumin and on Blood Anti-diuretic Hormone Concentration in Children With the Nephrotic Syndrome, Tr. Soc. Ped. Res., 1951; and Am. J. Dis. Child. **83:** 87, 1952.
7. Farnsworth, E. B., and Ruppenthal, B. A.: Electrophoretic Studies on Serum and Urine Protein in Nephrosis Treated With ACTH, J. Lab. & Clin. Med. **38:** 407, 1951.
8. Lenke, S. E., and Berger, H. M.: Abrupt Improvement of Serum Electrophoretic Pattern in Nephrosis After ACTH-induced Diuresis, Proc. Soc. Exper. Biol. & Med. **78:** 366, 1951.
9. Barnett, H. L., Forman, C. W., McNamara, H., McCrory, W., Rapoport, M., Mitchie, A. J., and Barbero, G.: The Effect of Adrenocorticotrophic Hormone on Children With the Nephrotic Syndrome. II. Physiologic Observations on Discrete Kidney Functions and Plasma Volume, J. Clin. Investigation **30:** 227, 1951.
10. Metcoff, J., Rance, C. P., and Nakasone, N.: Observations on Renal Mechanisms for Sodium and Potassium Excretion in ACTH-induced Diuresis of Nephrotic Edema, J. Clin. Investigation **30:** 661, 1951.

11. Kaye, I. A.: Determination of Total and Free Cholesterol in Blood Serum, J. Lab. & Clin. Med. **25**: 996, 1940.
12. Kingsley, M. S.: The Direct Method for the Determination of Serum Proteins as Applied to Photoelectric and Visual Colorimetry, J. Lab. & Clin. Med. **27**: 840, 1942.
13. Natelson, S.: Personal communication to the authors.
14. Sobel, A. E., Hirschman, A., and Besman, L.: Estimation of Ultra-microquantities of Urea and Kjeldahl and Amino Acid, Indust. & Eng. Chem. (Anal. ed.) **19**: 628, 1947.
15. Barnett, H. L., Forman, C. W., and Lauson, H. D.: The Nephrotic Syndrome in Children, Advances in Pediatrics, vol. V, p. 53.
16. Metcoff, J.: Proceedings of the Second Clinical ACTH Conference, vol. II, p. 155.
17. Bongiovanni, A. N., Blandheim, S. H., Eisenmenger, W. J., and Kunkel, H. G.: Effects of ACTH in Patients With Liver Disease, J. Clin. Investigation **29**: 798, 1950.
18. Fearnley, G.: Proceedings of the Second Clinical ACTH Conference, vol. II, p. 561.

THE PHYSIOLOGY AND DISORDERS OF CARBOHYDRATE METABOLISM

VICTOR A. NAJJAR, M.D.
BALTIMORE, MD.

IT IS a great privilege to contribute to this issue which is designed to honor Dr. Edwards A. Park. A good deal will be written about his outstanding qualities as a scientist, physician, teacher, and fisherman, endowed with a superb sense of humor. Unless this is done with a good measure of self-restraint it may well approach the flavor of hero worship because such is the man; his only fault is the lack of one.

I believe that one of his finest qualities is that of a counselor. Those of us who are close to him have sought his advice at every turn in the road. So generous and unerring his guidance has been that little of what we are and have accomplished can properly be called our own. This article is the direct product of his good counsel since upon his advice I set out to learn something about the enzymes involved in carbohydrate metabolism.

IN THIS field we now know most of the steps responsible for the breakdown of glycogen to lactic acid and the synthesis of glycogen from the latter. The enzymes taking part in this breakdown and synthesis are also known and a great many of them well defined. There are precise methods for assay of these enzymes that are no more complicated than many methods in current use in most clinical laboratories. It becomes feasible then to make use of these methods and discoveries in order to shed more light, if possible, on the clinical problems at hand relating to carbohydrate metabolism. There are very gratifying indications that the pediatricians are becoming aware of the value of these contributions and are beginning to make use of them. It is the purpose of this paper to emphasize and accelerate this growing awareness by bringing together the pertinent contributions made in the basic science of carbohydrate metabolism and by attempting to relate them to the clinical problems we face.

I can foresee, with a good measure of satisfaction, a fruitful field in the study of the enzymatic constitution of tissue; no less fruitful than has been the study of the structural constitution of tissue since the advent of the staining technique.

This paper will necessarily be limited to those enzyme systems of carbohydrate metabolism that have a direct bearing on the clinical problems confronting the clinician. For the purpose of clarity the discussion of these problems will involve the following categories:

I. The key enzymes that take part in the transformation of glucose to glycogen and vice versa.

From the Department of Pediatrics, Johns Hopkins University School of Medicine, and the Harriet Lane Home, Johns Hopkins Hospital.

II. The influence of hormones upon these systems.

III. Diseases of carbohydrate metabolism and possible interpretation of the metabolic defect in terms of the role of enzymes and hormones.

I. THE KEY ENZYMES OF GLUCOSE METABOLISM

As glucose enters the cell it is immediately phosphorylated. As the occasion demands, it may be synthesized into glycogen or broken down to a great number of intermediates and oxidized to carbon dioxide and water.

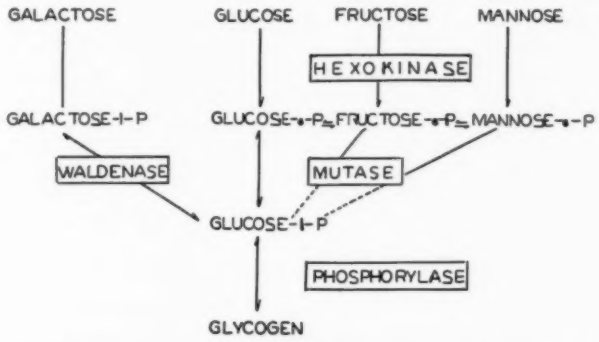

Fig. 1.—Showing the steps in the transformation of the monosaccharides to glycogen through glucose-1-phosphate and the enzymes involved in these steps.

The latter alternative supplies the body with the energy and heat required for normal physiological processes. The former is a storage mechanism whereby glucose is stored as glycogen. When the flow of glucose into the cell is not sufficient for normal requirements, glycogen is then called upon to replenish the necessary amount of glucose in order to maintain the metabolic activities of the cell.

The two substantial stores of glycogen in the body are in the liver and in muscle tissue. Although glycogen is stored in either tissue for the same ultimate purpose of acting as an energy reserve, there is one difference of major importance. The glycogen of muscle is stored for the single purpose of supplying energy only to muscle. Under ordinary circumstances it does not share its hoard of energy with other tissues, except through the formation of lactic acid which is rebuilt into glycogen in the liver, and to very minor degree during the action of 1,6-glucosidase on glycogen.[1] By contrast, the liver stores its glycogen for its own use as well as for distribution in the form of glucose to other tissues including muscle tissue. It is well to stress at this point that the level of blood glucose is regulated mainly by the liver. Even the transformation of proteins and fats into carbohydrates must undergo a rebuilding process in the liver before their ultimate conversion to glucose. This serves to explain, in part, the major cause of the grave disturbances in carbohydrate metabolism accompanying liver disease, as compared to the minimal effects accompanying disease of the muscles. This is best illustrated by the two main forms of glycogen disease. Here, although the net result is the accumula-

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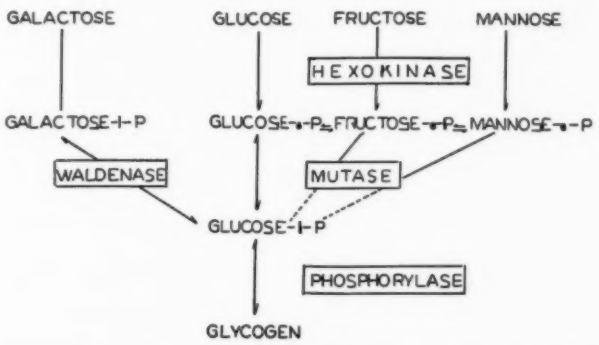

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The two substantial stores of glycogen in the body are in the liver and in muscle tissue. Although glycogen is stored in either tissue for the same ultimate purpose of acting as an energy reserve, there is one difference of major importance. The glycogen of muscle is stored for the single purpose of supplying energy only to muscle. Under ordinary circumstances it does not share its hoard of energy with other tissues, except through the formation of lactic acid which is rebuilt into glycogen in the liver, and to very minor degree during the action of 1,6-glucosidase on glycogen.[1] By contrast, the liver stores its glycogen for its own use as well as for distribution in the form of glucose to other tissues including muscle tissue. It is well to stress at this point that the level of blood glucose is regulated mainly by the liver. Even the transformation of proteins and fats into carbohydrates must undergo a rebuilding process in the liver before their ultimate conversion to glucose. This serves to explain, in part, the major cause of the grave disturbances in carbohydrate metabolism accompanying liver disease, as compared to the minimal effects accompanying disease of the muscles. This is best illustrated by the two main forms of glycogen disease. Here, although the net result is the accumula-

tion of glycogen, the type involving the liver is accompanied by far more severe disturbances in metabolism than the type involving muscle tissue.

Fig. 1 shows the major enzymes involved in the transformation of glucose, fructose, and galactose into glycogen. As is apparent, the first step in this transformation is a phosphorylation by the hexokinase enzymes. Since glucose is the main form of carbohydrate utilized it will serve as the main point of the discussion. Suffice it to say that galactose is phosphorylated to give galactose-1-phosphate, which is converted by the Waldenase enzyme to glucose-1-phosphate, at which point it follows the pathways of glucose. Fructose is equally phosphorylated to produce fructose-6-phosphate or fructose-1-phosphate, depending on the tissue in question. This is converted by the other enzymes into glucose-6-phosphate. At this point, it too follows the pathways of glucose metabolism to form glycogen, a branched polysaccharide, as seen in Fig. 2. A number of these enzymes have been crystallized from animal tissues and their properties well studied. Phosphorylase was crystallized by Green and associates[2] and phosphoglucomutase by Najjar.[3]

The process of phosphorylation of sugars can be viewed, with some justification and in the interest of simplification, as a process of activation. Consequently, both glycogen and glucose are not metabolically efficient until they are phosphorylated (Fig. 2).

In the scheme of glucose metabolism there are three steps where an unphosphorylated molecule becomes phosphorylated. One step is at the triose stage, where pyruvate becomes phosphopyruvate. This step will not be dealt with at this time. The other two steps are at the hexose stage, namely, the conversion of glucose to glucose-6-phosphate by the hexokinase enzyme and glycogen to glucose-1-phosphate by phosphorylase. For a profitable study of the mode of regulation of carbohydrate metabolism, one can, with a good deal of justification, search for regulatory mechanisms involving these steps, since each step is the first step in activating the molecule concerned and introducing it into the main chain of events that follow. Each step is also a final step in the opposite direction, i.e., inactivating the molecule and withdrawing it from the main chain of events. We are not ignoring the fact that glucose can be oxidized to gluconic acid, pyruvic acid reduced to lactic

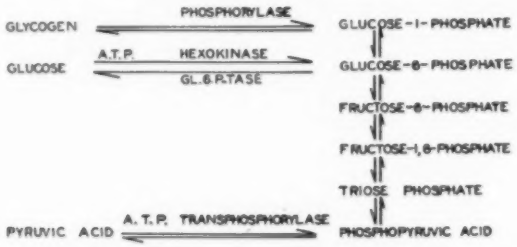

Fig. 2.—Showing some of the steps in the transformation of glycogen to pyruvic acid. The reactions shown horizontally are the main phosphorylative steps.

acid, and glycogen split by amylase, all without the intervention of phosphorylation. However, these are of minor quantitative significance in metabolism.

It thus appears that these three points may be the points of attack of regulatory influences hormonal or otherwise. Recent work strongly suggests that hormones act on enzyme systems and thereby direct the course of metabolism in the body. There are many mysterious and unexplained aspects of this problem which are no less challenging. Nevertheless, a new chapter in the field of science is beginning to unfold as more facts accumulate regarding the action of hormones on enzyme systems.

II. THE INFLUENCE OF HORMONES ON THE ENZYME SYSTEMS OF GLUCOSE METABOLISM

A. *The Influence of Hormones on the Hexokinase Enzyme.*—

The influence of insulin on the overall metabolism of carbohydrates has been known for a long time. There is little doubt that it improves the utilization of glucose, promotes its uptake from the blood stream, and increases its deposition as glycogen. This by no means explains all the manifestations of the diabetic state, nor the complete action of insulin. Feller and collaborators[4] showed that the oxidation of glucose to CO_2 is only slightly impaired in diabetes and the diabetic state cannot, therefore, be explained solely on the basis of impairment of removal of glucose from the blood stream.

The study of the effect of insulin on the isolated tissue was initiated by Gemmill and co-workers[5, 6] who showed that insulin aids in the deposition of glycogen from glucose in the isolated rat diaphragm. Subsequently, Colowick and associates[7] showed that in cell-free tissue extract insulin has a very definite effect. Measuring the activity of the hexokinase enzyme which phosphorylates glucose, they found that this reaction is inhibited in diabetic animals and that this inhibition can be counteracted by insulin. This marks the first and still the only instance where it was shown that a hormone can act in the absence of cell structure. This work was later extended by studying the hormonal effects on the hexokinase reaction in the more stable system of intact muscle tissue.[8, 9] This reaction is the first step in the mobilization of glucose and its activity can be followed by measuring glucose uptake by the tissue.

Using this approach it was shown[8] that the hexokinase reaction was inhibited in diabetic animals. The degree of inhibition varied directly with the severity of diabetes, being more marked in more severely diabetic animals. This inhibition was overcome by insulin or by removal of the adrenal. It therefore appears that the adrenal secreted a hormone that influenced the hexokinase reaction in a manner antagonistic to that of insulin. Further extension of this work[9] showed that the pituitary had a controlling influence as well. It was shown that after removal of the pituitary the hexokinase reaction showed increased activity, over 1.5 times that obtained when the pituitary is intact (Fig. 3).

It has been estimated[10] that one molecule of insulin, acting on the hexokinase of muscle diaphragm, mobilizes 2×10^8 molecules of glucose per hour at 37° C. Along with the uptake of glucose there is a concomitant uptake of potassium. This serves to illus-

trate further[11] the role of metals in enzyme reactions and their indispensability to metabolism.

Lately, it was shown that adrenaline acts on the hexokinase reaction also though in an indirect manner.[12] It inhibits glucose utilization, seemingly by suppressing the synthesis of adenosinetriphosphate (A.T.P.).

It appears from the foregoing that the hexokinase, as measured by glucose uptake by muscle tissue, is under the influence of pancreatic, adrenal, and pituitary hormones. Insulin promotes the utilization of glucose by stimulating the hexokinase reaction or by removing the inhibition produced directly or indirectly by the adrenal and pituitary glands. The pituitary hormone responsible for the direct inhibition caused by the pituitary appears to be the growth hormone.[13, 14] Thus insulin and the growth hormone have antagonistic properties relative to their effect on carbohydrate metabolism. In view of this one wonders whether the unopposed action of the growth hormone of pregnant diabetic mothers is responsible for the constant finding of larger babies born to diabetic mothers.

For the control of glucose utilization, which directly affects the blood glucose level, the organism is therefore dependent on opposing hormonal forces. A blood sugar rise of the diabetic type would result from a decrease in available insulin, as in diabetes, or an increase of available pituitary or adrenal hormones as obtains in hyperplasia or tumor, as often seen in Cushing's syndrome. This explains why this type of hyperglycemia is resistant to insulin. On the other hand, a low blood sugar would result from hyperinsulinism as in hyperplasia and adenoma of the pancreas, or from destructive processes affecting the pituitary or adrenal as found in Addison's disease.

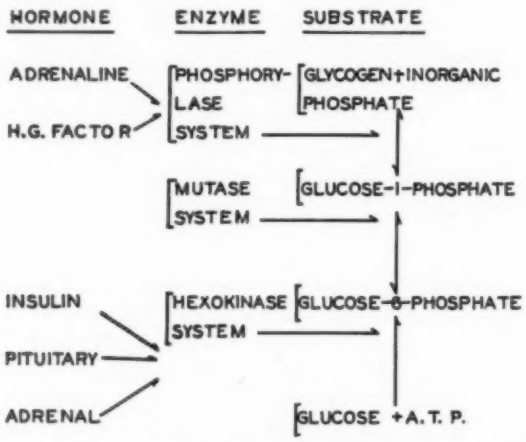

Fig. 3.—Showing the principal steps in the transformation of glucose to glycogen, the enzyme systems that motivate each step, and the hormones affecting those enzyme systems.

B. *The Influence of Hormones on the Phosphorylase Enzyme.*—

It is perhaps fortunate that the hormonal influence on carbohydrate metabolism is not limited to a few hormones acting on a few enzyme systems. The greater the complexity, i.e., the

greater the number of hormones acting on numerous targets in the enzyme systems, the greater the adaptability and versatility of the body. This ingenious foresight of nature was well calculated to protect us and not merely to confuse us as we are so often prone to believe.

Phosphorylase is the enzyme that breaks down glycogen to glucose-1-phosphate. It is also a key enzyme in the sense that it is the first enzyme that activates glycogen by phosphorylation and makes it possible for the phosphorylated molecule to proceed further in the metabolic path. Sutherland and Cori[15] described a pancreatic fraction which they termed hyperglycemic-glycogenolytic factor (H-G) that was present in insulin preparations and acted on phosphorylase in such a manner as to increase the breakdown of glycogen to glucose (Fig. 3). This was described earlier by Burger and Brandt[16] as glucagon and shown to be a protein distinctly different from insulin in its chemical behavior. This subject was recently reviewed by de Duve,[17] an early contributor in this field.[18] This factor is formed apparently by the alpha cells of the pancreas as well as in the argentophilic cells of the gastrointestinal mucosa.[17, 19] It is present in most insulin preparations used in this country and explains the initial rise of blood sugar upon injection of insulin and the glycogenolytic effect of large doses of insulin observed by Bridge[20] and others.[17] Sutherland and associates[21] purified this new hormone from dog pancreas and gastric mucosa. It was further shown that this factor stimulates the phosphorylase activity[22] by converting the inactive form of the enzyme to the active form (Fig. 4). This must involve two additional enzymes, one that activates and another that inactivates phosphorylase. A similar effect was found to be exerted by epinephrine. What seems to be disturbing and difficult to reconcile in this connection is that the site of action, i.e., phosphorylase, is a reversible system. It would be more comprehensible if the target, like the hexokinase, was an irreversible system. An intact cell system, however, is necessary as neither epinephrine nor the hyperglycemic factor act in cell-free state.

For regulation of blood sugar, one must now add these two factors acting on the phosphorylase system. When

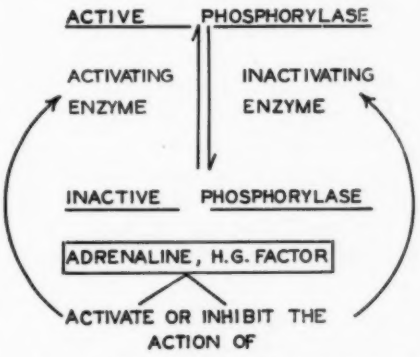

Fig. 4.—Showing the mode of action of adrenaline and H-G factor affecting the balance between active and inactive phosphorylase.

these are secreted into the blood stream they stimulate the enzyme that activates phosphorylase. In either case the net result is an increase in phosphorylase activity which through some mechanism increases the breakdown of glycogen to glucose. When, on the other hand, the blood sugar level is high, there is no flow of either adrenaline or the hyperglycemic factor, the net result being a diminution of active phosphorylase and an inhibition of breakdown of glycogen to glucose

which amounts to a shift of the equilibrium toward the conversion of glucose to glycogen. The action of the H-G factor is limited to the liver, whereas adrenaline stimulates glycogen breakdown in muscle as well. This explains the rise of lactic acid in the blood following adrenaline injection and the lack of such a rise following the administration of H-G factor,[19]

III. DISEASES OF CARBOHYDRATE METABOLISM AND POSSIBLE INTERPRETATION OF THE DEFECT IN TERMS OF THE ROLE OF ENZYMES AND HORMONES

A. *Diabetes* has remained a metabolic problem in spite of the relative success of insulin therapy. There are complications that befall the diabetic despite successful insulin therapy. Furthermore, neither the presence of diabetes nor the severity of the disease has been satisfactorily correlated with the functional state of the beta cells of the islet tissue. There is no doubt that insulin is secreted by those cells. A number of states simulating the hyperglycemic diabetic picture can be readily pictured from the preceding considerations. As stated previously, hyperglycemia can be caused by a suppression of insulin production or overstimulation of the pituitary or adrenal with no change in the available insulin. The over-all picture in either case adds up to an inhibition of the hexokinase reaction. One can also obtain a picture of hyperglycemia through overstimulation of the phosphorylase system. This may be the result of a hypersecretion of the alpha cells of the islets or hyperactivity of the adrenal medulla. The same picture can then be produced by hormonal action of different glands acting on two different key enzyme systems. Also, as one can readily surmise, the same endocrine gland may possess synergistic or opposing hormones. The islet tissue of the pancreas contains the beta cells producing insulin and the alpha cells producing the hyperglycemic factor. The adrenal, on the other hand, contains cortical hormones and adrenaline, both antagonizing insulin action. This is of practical consideration, since destructive lesions of the endocrine glands may result in opposite metabolic disturbances or accentuated derangement of carbohydrate utilization.

In the untreated diabetic state where the patient's own insulin activity is low, the high blood sugar level tends to depress the secretion of the hyperglycemic factor, as well as the pituitary and adrenal hormones. In essence then the diabetic is deficient not only in insulin but in the other hormones as well. As insulin therapy is instituted, the normal physiological balance is reached between the opposing hormones. This may explain the relative hypersensitivity of the untreated diabetic to insulin in some cases, as compared to their tolerance after maintenance therapy has proceeded for some time. Overtreatment with insulin is bound to be counteracted by overproduction of pituitary and adrenal hormones with the result that the requirement for insulin increases. Because of all these considerations one cannot overemphasize the importance of careful graduated treatment with insulin.

B. *Spontaneous or Recurrent Non-Addisonian Hypoglycemia* is another major disease of carbohydrate metabolism that we encounter in pediatrics. A number of possible causes might be formulated on the basis of the preced-

ing discussion. Hypersecretion of insulin caused by adenoma, tumor, or hyperplasia of the beta cells produces a picture of hypoglycemia with subnormal fasting blood sugar levels, and low glucose tolerance curves. However, hypofunction of the alpha cells or their absence produces a picture not unlike this. McQuarrie and his colleagues[23, 34] have recently shown that some cases of hypoglycemia show total or almost total absence of alpha cells in the pancreas. There are also other possibilities. Hypofunction of the pituitary or adrenal leave insulin unopposed in its action and cause a picture of hypoglycemia.

The common practice, heretofore, of removing a part of the pancreatic tissue cannot be expected to effect a cure, unless by so doing one removes a tumor. We have the means and we should explore such cases in order to determine the etiology. If the deficiency lies in the alpha cells, then treatment with the hyperglycemic factor (H-G factor) is as indicated as insulin is in the treatment of insulin deficiency diabetes. If hypofunction of the adrenal is present, then stimulation of those glands with adrenocorticotropic hormone is indicated.

The successful treatment of H-G factor deficiency hypoglycemia with ACTH[23] is explicable on the basis of stimulation of excessive adrenal hormones which in turn counteract insulin. This at present is the best form of therapy due to the unavailability of the H-G factor. When that becomes available it will certainly be the only specific form of substitution therapy, as it will be free of the known side effects of ACTH.

No doubt states of hypoglycemia may arise not only from hormonal imbalance but also from enzymatic defects, such as a defect in the enzymes that take part in the breakdown of glycogen to glucose, particularly glucose-6-phosphatase.

C. *Glycogen Storage Disease* is yet another disease that falls within the realm of anomalies of carbohydrate metabolism. In this disease there is storage of large quantities of glycogen in tissues and an over-all inability to break down glycogen to glucose. There are two types of this disturbance depending on the localization of the defect. The hepatic type represents glycogen storage in the liver and the cardiac type in the muscles of the heart and skeleton. The symptoms of the hepatic type are more severe and generalized, inasmuch as the liver supplies glucose to all body tissues in the absence of intake. However, the glycogen stored in the muscles is used almost solely by the muscle tissue concerned. The defect in this disease may be due to: (1) abnormal glycogen, (2) a defect in hormones, or (3) a defect in the enzyme system.

1. *Glycogen* is a branched polysaccharide. Glucose units are attached together with 1-4 carbon linkage to form long chains of glucose molecules. Chains of definite lengths then branch off in a treelike manner through a 1-6 carbon link. The length of the chains and the number of the branches determine the type and nature of the glycogen formed.

The glucose chains are formed by the enzyme phosphorylase discussed earlier. The branches are formed by the action of an enzyme called the branching factor, and cleaved by the enzyme amylo-1, 6-glucosidase. Any disturbance in the factors affecting the relative activities of these enzymes

might produce an abnormal glycogen with atypical chain length or abnormal number of branches. Such an abnormal glycogen has been reported by Cori[24, 34] in a case of glycogen disease with cirrhosis of the liver.

2. *Hormonal* defects as a cause of this disease have not received adequate attention. We have made a follow-up study of one patient (Case 2) reported and studied extensively earlier by Bridge and Holt.[25] The diagnosis was confirmed by biopsy. He was then 5½ years old. When studied at the age of 12 years, he was normal in all respects with the exception of a large liver. He had normal fasting blood sugar levels on three consecutive days, his morning urine showed no acetone, and glucose tolerance curve was normal.[27] At that time his activity was that of a normal child and his diet was unrestricted. He was also past the early stages of puberty. It is assumed that as this child grew older, toward puberty, certain hormonal adjustments took place that corrected the deficiency. The large liver may be due to some cirrhosis or to the fact that there still is storage of the abnormal glycogen formed prior to correction of the disturbance.

It is not easy to place the blame on any one hormone but a total absence of the hyperglycemic factor (H-G) with low hexokinase activity might explain most of the manifestations. It will be very profitable to observe the effect of H-G factor therapy in such cases.

3. *Enzymatic defect.* This has been discussed by di Sant' Agnese and coworkers.[26] If an enzymatic defect exists, it is more likely than not to involve more than one enzyme, since other defects such as that of methylation occur.[28] The key enzymes in the breakdown to glucose are, as we noted earlier, phosphorylase and the specific glucose-6-phosphatase of de Duve.[29] The defect may then be in the formation of active phosphorylase from the inactive form. A diminished amount of phosphorylase activity may explain the slow uptake of glucose sometimes observed, with a limited ability to break it down. If both of these reactions are of the same order of magnitude, one would still obtain a picture of glycogen storage with hypoglycemia. The reason for this becomes apparent when one recognizes that glycogen synthesis need not be a quick process. If glucose is not taken up for quick storage, it will remain in the blood stream until it is eventually taken up. However, the demand for glucose is always rapid since any demand occasioned by muscular exercise should be met with an immediate glycolytic response. Failing that, hypoglycemia develops with its attending symptoms. In general, such cases do not show complete absence of glycolysis, and this would be in keeping with this possibility.

Another possible defect is in the glucose-6-phosphatase enzyme as shown by Cori.[34] This is the enzyme that is concerned with the last step of furnishing glucose. A defect in this enzyme or its absence can explain most of the manifestations. There is one point that must be stressed, i.e., the absence of this enzyme in muscle tissue. It is unlikely that the enzyme phosphoglucomutase, intervening between these two key enzymes, would play a role.

D. *Galactosemia and Galactosuria* is a disease entity that shows, in effect, an inability to metabolize galactose. Recent suggestions[30] regarding the

cause of the disease do not fit into our present knowledge of carbohydrate metabolism.

This entity lends itself eminently for enzymatic study. Galactose must undergo two steps to enter the metabolic pathway of glucose as shown in Fig. 1. Galactose is acted upon by a specific hexokinase to form galactose-1-phosphate and the latter is changed to glucose-1-phosphate by the Waldenase enzyme. These steps have recently been elucidated by the Leloir group.[31-32]

CONCLUSION

From the preceding considerations of carbohydrate metabolism it seems clear that the biochemists have placed within our reach methods and means by which we are now able to study metabolic defects in the body.

There is no reason why the clinician should regard these enzyme systems as being outside his realm. The enzymes that take part in carbohydrate metabolism should become as familiar to us as trypsin, pepsin, lipase, and amylase have been for some time.

We believe that whenever there are indications for biopsy, in order to study the possible pathology in the structure of a tissue, there are for the same fundamental reason equally good indications for the study of the enzymatic constitution of the tissue.

REFERENCES

1. Cori, G. T., and Larner, J.: Amylo-1, 6-Glucosidase, Fed. Proc. **9**: 163, 1950.
2. Green, A. A., Cori, G. T., and Cori, C. F.: Crystalline Muscle Phosphorylase, J. Biol. Chem. **142**: 447, 1942.
3. Najjar, V. A.: The Isolation and Properties of Phosphoglucomutase, J. Biol. Chem. **175**: 281, 1948.
4. Feller, D. D., Strisower, E. H., and Chaikoff, I. L.: Turnover and Oxidation of Body Glucose in Normal and Alloxan-Diabetic Rats, J. Biol. Chem. **187**: 571, 1950.
5. Gemmill, C. L.: The Effect of Insulin on the Glycogen Content of Isolated Muscles, Bull. Johns Hopkins Hosp. **66**: 232, 1940.
6. Gemmill, C. L., and Hamman, L., Jr.: The Effect of Insulin on Glycogen Deposition and on Glucose Utilization by Isolated Muscles, Bull. Johns Hopkins Hosp. **68**: 50, 1941.
7. Colowick, S. P., Cori, G. T., and Slein, M. W.: The Effect of Adrenal Cortex and Anterior Pituitary Extracts and Insulin on the Hexokinase Reaction, J. Biol. Chem. **168**: 583, 1947.
8. Krahl, M. E., and Cori, C. F.: The Uptake of Glucose by the Isolated Diaphragm of Normal, Diabetic and Adrenalectomized Rats, J. Biol. Chem. **170**: 607, 1947.
9. Krahl, M. E., and Park, C. R.: The Uptake of Glucose by the Isolated Diaphragm of Normal and Hypophysectomized Rats, J. Biol. Chem. **174**: 939, 1948.
10. Willebrands. A. F., Groen, J., Kaminga, C. E., and Blickman, J. R.: Quantitative Aspects of the Action of Insulin on the Glucose and Potassium Metabolism of the Isolated Rat Diaphragm, Science **112**: 277, 1950.
11. Najjar, V. A.: The Influence of Inorganic Ions on Enzyme Reactions, McCollum-Pratt Symposium on Phosphorus Metabolism **2**: 500, 1951.
12. Cohen, J. A., and Needham, D. M.: The Effect of Adrenaline Injection in the Utilization of Glucose in Muscle Extracts, Biochim. et biophys. acta **6**: 141, 1950.
13. Park, C. R., and Krahl, M. E.: Effect of Pituitary Extracts Upon Glucose Uptake by Diaphragms From Normal, Hypophysectomized and Hypophysectomized-Adrenalectomized Rats, J. Biol. Chem. **181**: 247, 1949.
14. Cotes, P. M., Reid, E., and Young, F. G.: Diabetogenic Action of Pure Anterior Pituitary Growth Hormone, Nature **164**: 209, 1949.
15. Sutherland, E. W., and Cori, C. F.: Influence of Insulin Preparations on Glycogenolysis in Liver Slices, J. Biol. Chem. **172**: 737, 1948.
16. Burger, M., and Brandt, W.: Ueber das Glucagon (die Hypergly-kamisierende Substanz des Pankreas), Ztschr. ges. exper. Med. **96**: 375, 1935.
17. De Duve, C.: Le Principe Hyperglycemiant du Pancreas (Glucagon, Facteur H-G), Rev. méd. Liège **6**: 258, 1951.
18. Bouckaert, J. P., and de Duve, C.: The Action of Insulin, Physiol. Rev. **27**: 39, 1947.
19. Sutherland, E. W.: The Effect of the Hyperglycemic Factor of the Pancreas and of Epinephrine on Glycolysis, Recent Progress in Hormone Research, Proceedings of the Laurentian Hormone Conference **5**: 441, 1950.
20. Bridge, E. M.: The Action of Insulin on Glycogen Reserves, Bull. Johns Hopkins Hosp. **62**: 408, 1938.

21. Sutherland, E. W., Cori, C. F., Haynes, R., and Olsen, N. S.: Purification of the Hyperglycemic-Glycogenolytic Factor From Insulin and From Gastric Mucosa, J. Biol. Chem. **180**: 825, 1949.
22. Sutherland, E. W., and Cori, C. F.: Effect of Hyperglycemic-Glycogenolytic Factor and Epinephrine on Liver Phosphorylase, J. Biol. Chem. **188**: 531, 1950.
23. McQuarrie, I., Bell, E. T., Zimmermann, B., and Wright, W. S.: Deficiency of Alpha Cells of Pancreas as Possible Etiological Factor in Familial Hypoglycemosis, Fed. Proc. **9**: 337, 1950.
24. Cori, C. F.: The Metabolism of Disaccharides and Polysaccharaides, McCollum-Pratt Symposium on Phosphorus Metabolism **2**: 62, 1951.
25. Bridge, E. A., and Holt, L. E.: Glycogen Storage Disease, J. PEDIAT. **27**: 299, 1945.
26. Di Sant' Agnese, P. A., Andersen, D. H., Mason, H. H., and Bauman, W. A.: Glycogen Storage Disease of the Heart, Pediatrics **6**: 402, 1950.
27. Najjar, V. A., and Hall, R. S.: Unpublished observations.
28. Najjar, V. A., Hall, R. S., and Deal, C. D.: A Simple and Practical Test for Liver Function, Bull. Johns Hopkins Hosp. **76**: 83, 1945.
29. De Duve, C., Berthet, J., Hers, H. G., and Dupret, L.: Le Système Hexose-Phosphatasique. Exixtence d'Une Glucose-6-Phosphatase Specifique dans le Foie, Bull. de la Soc. de Chim. Biol. **31**: 1242, 1949.
30. Mellinkoff, S., Roth, B., and MacLaggan, J.: Galactosemia With Hepatic Damage, J. PEDIAT. **27**: 338, 1945.
31. Trucco, R. E., Caputto, R., Leloir, L. F., and Mittleman, N.: Galactokinase, Arch. Biochem. **18**: 137, 1948.
32. Caputto, R., Leloir, L. F., Trucco, R. E., Cardini, C. E., and Paladini, A. C.: The Enzymatic Transformation of Galactose Into Glucose Derivatives, J. Biol. Chem. **179**: 497, 1949.
33. Greenman, L.: Alterations in Blood Glucose Following Intravenous Galactose, J. Biol. Chem. **183**: 577, 1950.
34. Najjar, V. A., Editor: A Symposium on Carbohydrate Metabolism, Baltimore, 1952, The Johns Hopkins Press.

VITAMIN D INTOXICATION IN INFANCY

A Report of Four Cases

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Montreal, Canada

THE discovery by Windaus and Hess[1] and Rosenheim and Webster[2] in 1927 that irradiated ergosterol possessed marked antirachitic properties led to the extensive use of this substance as an antirachitic agent. At the same time, it resulted in studies of the action of this form of vitamin D in large doses in experimental animals. The first reports of toxic effects of this substance were made by Pfannensteil[3] in 1927 and Kreitmar and Moll[4] in 1928. These findings were amply confirmed and extended by others. Summarized briefly, the toxic effects of overdosage in animals are as follows: There is anorexia, loss of weight, diarrhea, loss of activity, and extreme weakness. Sometimes paralysis of the limbs is noted. The urine contains albumin and an excess of calcium salts. The blood shows hypercalcemia and frequently hyperphosphatemia. There is increased absorption of calcium and phosphorus from the gut. By reducing the calcium in the diet the symptoms of intoxication are diminished. At first there is an increased deposition of calcium salts at the provisional zone of calcification and increased mineralization of the bone trabeculae. If the hypervitaminosis is prolonged and of sufficient severity, increased excretion of calcium by the kidney follows and the calcium and phosphorus retention in the body is decreased. At the same time, metastatic calcification of different organs of the body develops, namely, in the media of the blood vessels, the kidneys (especially the tubules), the heart, the stomach wall, the alveoli of the lungs, the bronchi, and the adrenals. Certain degenerative changes in the media of the blood vessels and in the kidney cells suggest that these are primary and the metastatic calcification secondary. There is a decrease of bone ash, particularly on a low calcium diet. The rarefaction of the compact and spongy portion of the bone suggests that this acts as a reservoir from which calcium is supplied for the phenomenon of metastatic calcification. This resorption of spongy bone is frequently most marked just proximal to the dense zone of provisional calcification.

There have been a number of reports of vitamin D intoxication in adults and children. The literature on this subject has been carefully reviewed by Anning, Dawson, Dolby, and Ingram[5] up to 1948. Up to that year they reported fourteen fatal cases of which six occurred in infancy. Since then Debré[6] has reported having had a series of twenty-one cases in children, with two fatalities. The present report which was the subject of a preliminary communication in 1939[7] was prompted by the occurrence of four cases in infancy within three months in our clinic. These patients all received a highly potent prepara-

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tion of irradiated ergosterol containing 56,000 international units of vitamin D per gram.* This was given in excess over prolonged periods. Two of these patients recovered and one of these was kept under prolonged observation for months. Two died and one of these came to post-mortem examination and showed the typical findings of the malady. The case reports of these patients follow:

Fig. 1.—Case 1, R. V. X-ray of forearm, hand, and knee.

CASE REPORTS

CASE 1.—R. V., female, 14 months of age, was admitted to hospital March 21, 1938, with the following complaints: fever for three months, anorexia, irritability, loss of weight, vomiting, frequency of urination. The patient had been a full-term infant, artificially fed. From the age of 2 months to one year she received 10,000 I.U. of irradiated ergosterol. For the past two months she had been receiving 30,000 units daily. Whooping cough developed three months previous to admission and the above-mentioned symptoms had developed during that period. The physician had found casts in the urine on several occasions previous to admission. Examination revealed an irritable, marasmic, asthenic, hypotonic infant weighing 14 pounds, with a temperature of 101° F. She was lying in bed with the legs abducted. She was unable to stand, even with support. There was marked hypotonicity of the muscles but the deep reflexes were present. There was a slight left-sided peripheral facial palsy. The physical examination otherwise showed no abnormalities. The urine showed three plus albumin, hyaline casts, and some pus cells with clumping. The red blood count was 3,120,000, white blood count 17,300; hemoglobin 65 per cent, sedimentation rate 40 corrected. Blood nonprotein nitrogen was 44.4 mg. per cent. At this time the impression was that the child was suffering from a nephritis or pyelonephritis, or some obscure infection. On March 26 further tests on the blood showed the following: nonprotein nitrogen 37.7 mg. per cent, creatinin 1 mg. per cent, serum calcium 17.8 mg. per cent, inorganic phosphorus 6.9

*Through the kindness of Dr. E. A. Park a sample of this material was tested by Dr. Bills and found to contain no toxisterol.

mg. per cent, alkaline phosphatase 18.2 units. Repeat tests on March 28 showed serum calcium 17.8 mg. per cent, inorganic phosphorus 6.9 mg. per cent. The finding of a hypercalcemia prompted investigation and inquiry revealed that vitamin D had been taken in large doses. Radiological examination revealed the following findings: skull normal, no renal calculi, all the long bones, including the ribs, the bones of the pelvis, and the scapulae and clavicles, showed extreme thickening of the periosteum. The ends of the long bones showed no widening or cupping. A very heavy line was present at the ends of the long bones indicating excessive calcification at the provisional zone of calcification. Proximal to this zone of increased density was a broad area of rarefaction indicating decalcification. Proximal to this appeared another area of increased density. There were no scattered areas of rarefaction. Reproductions of this phenomenon are shown in x-rays of the forearms, hands, and knees (Fig. 1).

It was felt that this child was probably suffering from vitamin D intoxication rather than primary or secondary hyperparathyroidism. The administration of vitamin D was discontinued and the calcium excretion was measured on normal and low calcium intake. Tables I, II, and III indicate the urinary calcium excretion during three periods. It will be observed that during the first period the urinary calcium excretion was high. During the second period even while on a relatively high calcium diet the calcium excretion was low. This is difficult to explain. During the third period on a very low calcium intake the urinary calcium is still high. This is explicable if one observes the persistently high serum calcium during this period as will be seen in Table IV. During the first month's stay in hospital the child remained irritable, weak, refused feedings, vomited frequently and required gavaging. However, following this, the child's condition gradually improved. She became more cheerful and her appetite improved. The urine showed only one plus albumin and the pus cells and casts had almost disappeared. She was discharged on June 9. During the summer her condition improved steadily and she remained in good health. In September her serum calcium was normal and her urine was clear. She was showing a normal weight gain. In March, 1939, one year after her admission to hospital, x-rays of her bones showed that they were normal.

TABLE I

DATES	URINE VOLUME	CREATININ (MG.)	CALCIUM (MG.)
April 2	585	69	74
April 3	550	71	104
April 4	590	74	81
Daily calcium intake 886 mg.			
Daily average excretion 86 mg.			

TABLE II

DATES	CREATININ (MG.)	CALCIUM (MG.)
May 13	78	19
May 14	48 (cloudy)	44
May 15	67	34
Daily calcium intake 826 mg.		
Daily average excretion 32 mg.		

TABLE III

DATES	URINE VOLUME	CREATININ (MG.)	CALCIUM (MG.)
May 26	395	68.2	69.1
May 27	675	75.2	91
Daily calcium intake 66 mg.			
Daily average excretion 80 mg.			

TABLE IV. SERUM CALCIUM AND INORGANIC PHOSPHORUS

DATES	CALCIUM MG. %	PHOSPHORUS MG. %
March 26	18	5.1
March 28	17.8	6.9
April 11	13.2	9.4
April 24	14.9	5.3
May 17	13.4	4.8
May 30	14.7	3.5
Sept. 13	11	

CASE 2.—J. D., female, 8 months of age, was admitted to the hospital June 7, 1938, with the following complaints: anorexia, constipation, vomiting, and failure to gain. These symptoms had been present for from three to four months. The infant had been full term, and had been breast fed for three weeks. At the age of 3 months the child was started on 10,000 I.U. of irradiated ergosterol daily. At 4 months this was increased to 14,000 I.U. daily, and at 5 months a further increase to 30,000 I.U. daily was made on account of suspected rickets. This was continued up to 6 months at which time the dose was decreased again to 20,000 I.U. daily and kept at that level. Admission examination revealed a poorly nourished infant not appearing acutely ill. The spleen was just palpable; the osseous system appeared normal. The urine showed no albumin, white blood cells, or casts. The blood showed a moderate anemia. In view of the history of excessive vitamin D intake and the symptoms, vitamin D intoxication was suspected. The serum calcium was 18.7 mg. per cent. Repeat examination showed 19.3 mg. per cent and inorganic phosphorus 5 mg. per cent. X-rays of the long bones showed changes comparable to the first case but of a much slighter degree. Vitamin D was excluded from her diet, and the child was sent home. During the next two months her general condition improved steadily and since then her health has been good. In September, her blood was again examined and her serum calcium was 11 mg. per cent.

Fig. 2.—Case 3, J. P. X-ray of arms

CASE 3.—J. P., male, aged 10 months, was admitted to hospital May 9, 1938, with a diagnosis of pneumonia. The twin of this patient died on the day the patient was admitted. He also had pneumonia. He was asphyxiated by aspiration of a milk curd. A post-mortem examination was obtained which will be described later. The patient was one month premature, never breast fed. From the age of 2 to 6 months this infant and his twin had received 24,000 I.U. of irradiated ergosterol daily. From 6 to 8 months this had been increased to 40,000 units daily, as the infant seemed to have a rachitic rosary. From 8 to 10 months this was re-

duced to 20,000 I.U. daily. For some months the baby had shown a tendency to vomit and had gained slowly at first and later not at all. The patient had developed a cough and fever a week previously, and examination revealed bilateral bronchopneumonia. The urine showed one plus albumin. The infant was greatly emaciated, weighing 10 pounds 11 ounces. The blood showed 56 per cent hemoglobin. X-ray of the bones showed thickening of the periosteum. The ends of the radius and ulna showed no widening or cupping. A heavy line was present at the ends of these bones indicating excessive calcification at the proximal zone of calcification. Proximal to this was a broad area of rarefaction indicative of decalcification, and proximal to this another narrower area of increased density. The picture was comparable in all respects to that seen in Case 1 (Fig. 2). The patient's condition deteriorated steadily and he died on May 11. In view of the history and the x-ray findings a tentative diagnosis of vitamin D intoxication was made. The serum calcium was not determined.

Case 4.—B. P., a twin of the previously described patient, died at home on May 9. His history was practically identical with that of his brother, viz., the same feeding difficulties with a tendency to vomit and a very slow weight gain. He had received the same amounts of irradiated ergosterol as his brother. He had developed pneumonia and was doing fairly well when he died suddenly after a feeding. Post-mortem examination revealed the cause of death to have been asphyxia from the aspiration of a milk curd which had lodged in the trachea. Bronchopneumonia was also present. At the time of the post-mortem examination the pathologist did not have the history of excessive vitamin D intake, so that the bones were not systematically examined. However, no gross evidence of rickets was found. No parathyroid tumor was found. When the twin died and a full dietary history was obtained the organs were subjected to careful histological study and a complete report of the finding follows:

Heart: Sections from the left ventricle showed an intact pericardium. Many areas showed normal muscle fibers abruptly giving way to fibers in varying stages of degeneration. Usually this occurs in bundles but the individual atrophic fibers were visible under higher magnification. This was noticeable by the loss of definition of the nucleus, which became globular with its cytoplasm very pale. In addition the striations were completely lost. Fibrotic replacement in these regions was minimal, but did take place, for loosely arranged fibroblasts were present and the van Gieson preparation showed thin wisps of collagenous fibers intimately associated with them. More frequently in these areas of evident degeneration were seen clumps of amorphous blue-staining material, which deposited itself intra- but more often extracellularly. This was entirely apart from the periphery of regional small arterial branches. Deposition did take place in many of the coronary branches, however, and occupied the entire width of the vessel wall. In the medium-sized arteries, the pigment concentrated in the medial coat. Kossa's technique showed this pigment to be calcium (iron stains were negative). The endocardium was normal.

In the right ventricle the areas of degeneration and metastatic calcification were absent. The larger coronary branches contained a similar distribution of the calcium as in the left ventricle. The same remarks are true for the left auricle and appendages.

Vessels: The aorta had been studied at different levels. Very striking, in view of the calcification of other sections, was its complete failure of appearance here, except in an occa-

Fig. 3.

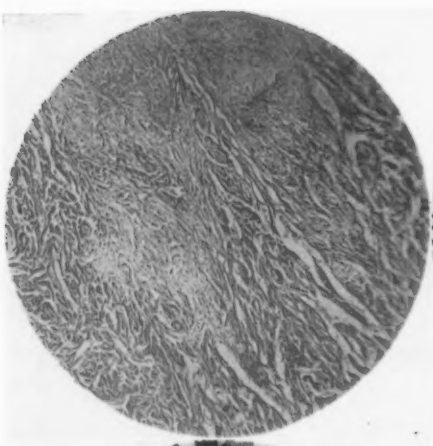
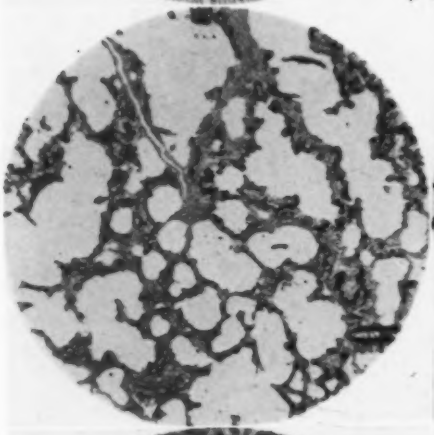


Fig. 4

Fig. 5.



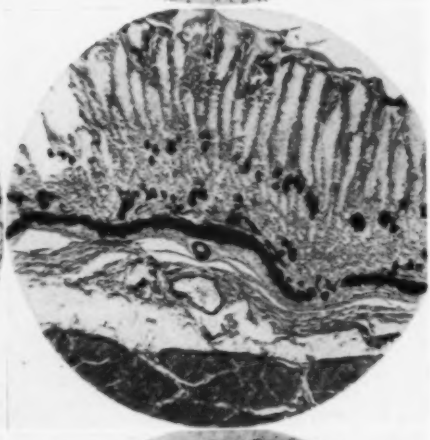


Fig. 6

Fig. 7.

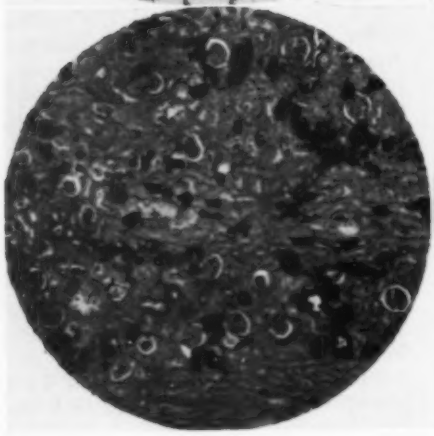


Fig. 8

Figs. 3-8.—*(For legends, see opposite page.)*

sional vasa vasorum. Furthermore, there was no indication that there had been any damage to collagenous or elastic fibers as a preliminary destruction prior to a possible calcification. Medium-sized vessels seen in branches supplying the adrenal gland and about the trachea, as examples of vessels of this type, had been studied for calcium distribution especially in elastic tissue preparations. The lining cells of the intima remained, and the concentration of calcium was chiefly in the media. In many of the viscera the smallest vessels, of arteriolar dimension, had some medial but chiefly periadventitial calcium accumulations. In the capillaries, especially in the lung parenchyma, the lumen is occasionally obscured by fine lines of calcium, although usually from compression by clumps of calcium, in and about septal and giant cells.

Lung: All of the lobes showed a representative histological picture. In addition to the precipitation in the capillaries, masses were present in the bronchial walls and beneath marginal epithelium. The cartilaginous plaques were heavily calcified. A localized productive interstitial pneumonic process created an area in which heavier calcium deposition was found in relation to the patchy fibroblastic proliferation.

Thymus, Thyroid, and Parathyroid: All sections from these glands were perfectly normal.

Spleen: Except for prominent calcium deposition, particularly in the intima in this organ, the sections showed only slight passive congestion. Iron stains were negative.

Pancreas; Adrenal: Normal.

Stomach: The calcium precipitation was quite heavy in this organ and was found in the basal portions of the epithelial cells comprising the mucosa. It also extended throughout the length of the muscularis mucosae. The other muscular layers were not involved. This is the manner of deposition in both pylorus and fundus.

Kidney: The glomerular tufts were for the most part well preserved, only infrequently being blurred by calcium. Afferent arterioles, small- and medium-sized vessels were free of it. The greatest calcium concentration is that which replaced convoluted tubular epithelium, at times filling the entire lumen. Not infrequently it formed in clusters and mantles about the glomeruli. The tubules in the pelvis had lesser concentrations, although many of them were completely obstructed by the calcium. It did not appear in the lining cells of the pelvis.

Liver, Abdominal Lymph Nodes, Testis: All were normal.

Ribs: Normal for age period with no evidence of early rickets.

Figs. 3 to 8 illustrate the histological lesions in some of the organs.*

The etiology of the disease in all four patients is obvious. They had each received a highly potent preparation of irradiated ergosterol, which did not contain toxisterol, in very large doses. The amount given daily varied between 30,000 and 40,000 I.U. over a period of months. This preparation contained 2,000 I.U. of vitamin D to the drop. In three of the patients rickets was suspected and

*We are much indebted to Dr. Stuart W. Lippincott for the thorough pathological study of this case.

Fig. 3.—Heart. Showing areas of degeneration. (Hematoxylin-eosin stain.)

Fig. 4.—Heart. Areas of degeneration as in Fig. 3 are present but in addition heavy deposition of calcium intra- and chiefly extracellularly. (Kossa stain, for calcium.)

Fig. 5.—Lung. Calcium fills many capillaries completely. It is also present in septal cells. (Kossa stain.)

Fig. 6.—Stomach. The calcium deposition is marked in the basal epithelial cells and muscularis mucosae but is absent in other muscle layers. (Kossa stain.)

Fig. 7.—Kidney. The convoluted tubular epithelium contains most of the calcium, occasionally the interstitial stroma, and rarely capillary tufts. (Hematoxylin-eosin stain.)

Fig. 8.—Small arteries. The intima is sharply delineated by the calcium. Heavier local deposits occur in the media. (Kossa stain.)

this was apparently the reason for increasing the already large dosage.

DIAGNOSIS

The presence of this disease should be suspected when a history of prolonged administration of high doses of vitamin D is accompanied by the previously mentioned symptoms. When hypercalcemia is present, the condition must be differentiated from hyperparathyroidism. This disease seldom occurs in infancy. In both conditions there is decalcification and increased calcium excretion by the kidney. Generalized skeletal osteoporosis occurs in both; but in hyperparathyroidism there are frequently cystic-like areas of rarefaction. The symmetrical areas of rarefaction proximal to the provisional zone of calcification are characteristic of hypervitaminosis D. In vitamin D intoxication there are also evidences of increased endochondral and periosteal calcification. These are not present in hyperparathyroidism. In vitamin D intoxication the inorganic phosphate is high whereas in hyperparathyroidism it is low. The above-mentioned facts as well as the history of the vitamin D intake serve to make the diagnosis clear.

SUMMARY

Four cases of hypervitaminosis D in infants have been presented, all of which showed the characteristic clinical picture. The radiological examination of the bones in two patients showed the typical appearance. The pathological study of the organs in one case demonstrated the phenomenon of metastatic calcification in certain organs of the body as well as degenerative changes in the heart muscle. Clinical evidence of renal damage was present in two cases. That the condition is reversible was shown by the recovery of the first two patients. In the first patient, after a prolonged period of reparation the kidney function and bone architecture returned to normal. The danger of high vitamin D administration over long periods is evident.

REFERENCES

1. Windaus and Hess: Proc. Soc. Exper. Biol. & Med. **24**: 369, 1927.
2. Rosenheim and Webster: Biochem. J. **21**: 389, 1927.
3. Pfannensteil: Klin. Wchnschr. **48**: 2310, 1927.
4. Kreitmar and Moll: München. med. Wchnschr. **75**: 637, 1928.
5. Anning, Dawson, Dolby, and Ingram: Quart. J. Med. **17**: 203, 1948.
6. Debré: Am. J. Dis. Child. **75**: 787, 1948.
7. Ross and Williams: Am. J. Dis. Child. **58**: 666, 1939.

RENAL FUNCTION STUDIES IN ACUTE GLOMERULONEPHRITIS IN CHILDREN

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IN THE course of our investigations in children with acute glomerulonephritis, studies were made to determine the nature of renal functional disruption and its duration. Using the methods of renal clearance of Homer Smith and his associates, it was hoped that more precise knowledge of the basic physiologic disturbances in acute glomerulonephritis could be defined. These studies are an extension of some preliminary observations begun in 1945[1] and are in general agreement with several reported studies.[2-8]

In all, thirty children were studied by these clearance methods. The typical clinical picture of acute glomerulonephritis was present in each case. Table I lists the findings. All but one of the children recovered from their acute disease; one child died in uremia thirty days after the onset of his disease. The ages of these children ranged from 2 to 15 years with an average age of 7.6 years. The group comprised twenty-one boys and nine girls. Ten patients were observed at the Philadelphia Children's Hospital and twenty at the Buffalo Children's Hospital.

The glomerular filtration rate was determined by mannitol clearance using the single injection technique; renal plasma flow was estimated simultaneously as the clearance of PAH at low plasma levels; Tm_{PAH} was determined immediately following the estimation of renal plasma flow, and urea clearance was determined simultaneously with the G.F.R. The details of the techniques used and the methods of analyses are described in a previous publication.[9] All values recorded in the tables and charts are corrected to 1.73 sq. M surface area.

In all but two cases (Cases 7 and 18) the G.F.R. was reduced at the time of the first observation (Fig. 1). The mean value for the G.F.R. during the first nineteen days of the disease was 72.2 c.c./min./1.73 sq. M (normal mean value 130.2) (see Table II). The difference between the mean of this group and one of normal children is 7.7 times its standard error and, therefore, highly significant. In nineteen of these patients studied between the twentieth and eighty-ninth day of their illness, the mean G.F.R. was 90.5 c.c./min./1.73 sq. M. This was still significantly below the normal values but significantly higher than the mean of values during the first nineteen days (see Table

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We should like to extend our thanks to the Sharp and Dohme Company of Glenolden, Pa., for generously supplying us with mannitol and sodium para-aminohippurate acid used in these studies.

TABLE I. LABORATORY DATA AND CLINICAL OBSERVATIONS

NAME & SEX	AGE (YR.)	DAY OF ILLNESS	B. P.	EDEMA	SED. RATE MM./HR.	URINE			G.F.R.	UREA CL.	R.P.F.
						SP. GR.	ALB.	R.B.C.	C.C./MIN./1.73 SQ.M.		
1. T. M. ♂	9	2	105/60	0	28	1020	4+	2-20/hpf	4.3	1.0	
		180	110/70	0	5	1018	0	3.8 M/12 h.	61		891
2. F. J. ♂	3¾	4	140/100	1+		1020	1+	Loaded	44		523
		39	100/60	0	28	1015	Trace	10-15/hpf	114		798
3. S. P. ♀	9¾	4	168/118	2+	46	1003-1018	2+	Many	102	43	884
		14	120/70	0	58	1008	0	0	99	79	984
4. P. S. ♂	3½	5	122/86	1+		1016	4+	20-30/hpf	49	28	659
5. P. M. ♂	3½	6	122/84	1+		1018	2+	40-50/hpf	90.5	37	836
6. R. L. ♂	13	6	140/90	1+	35	1008	4+	20-30/hpf	40	25	848
		24	120/70	0	35	1014	1+	5-10/hpf	77	50	743
		89	130/76	0	23	1032	0	8.0 M/12 h.	110	57	761
7. E. T. ♀	12	7	120/90	Trace	24	1015	2+	Many	125.5	72	724
		17	114/58	0	13	1018	±	3-5/hpf	131	83	819
8. H. H. ♂	8¾	7	150/100	0	22	1001	2+	30-50/hpf	71	51	763
		24	120/56	0	28	1018	0	0-1/hpf	76	56	629
		40	124/56	0	7	1023	0	3.8 M/12 h.	88.5	63.5	772
9. A. R. ♂	4 11/12	7?	130/76	1+	22	1021	2+	5-10/hpf	49(I)	31	439
10. G. S. ♂	6	9	130/80	2+	24	1012	2+	Many	54		612
		22	100/60	0	22	1031	Trace	Many	63		
		79	100/50	0	5	1020	0	19 M/12 h.	138	92	920
11. M. L. ♀	2½	9	100/70	0		1030	2+	30-40/hpf	73		636
		25	94/68	0	30	1020	0	0	67		393
12. R. G. ♂	6½	9	135/85	1+	31	1004	Trace	10-15/hpf	82	63.5	573
		27	114/60	0	22	1004	0	3-5/hpf	118	60	785
13. E. Mc. ♂	3½	9	95/50	0			2+	Loaded	63		758?
		80	110/60	0	17	1020	0	1.03 M/12 h.	102		544
14. T. H. ♂	6½	10	110/60	0	48	1007	0	3-6/hpf	100.5	65	633
15. B. S. ♂	7	10	100/80	0		1012	0	0	56.5		
16. Y. G. ♀	7	10	110/90	0	59	1012	3+	20-30/hpf	48(I)	25	611
		40	110/70	0	54	1014	1+	2-3/hpf	85	62	686
		90	108/74	0	23	1008	1+	6.4 M/12 h.	115	64	723
17. R. Sc. ♂	8¾	11	128/76	Trace	8	1016	4+	5-10/hpf	65	37	381
		34	124/74	0		1012	1+	0	114	64	553
18. T. T. ♂	11	12	144/96	0	43	1025	1+	30-40/hpf	124	65	>488
19. J. L. ♂	4	14	120/70	0	24	1010-1031	Trace	10-15/hpf	57		410
		99		0		1020	0	1.3 M/12 h.	89.5		478

Note. In Cases 9, 16 (first test), and 22 the glomerular filtration rate was determined with inulin instead of mannitol. This is indicated by (I) after the figure for G.F.R.

Abbreviations:
B.P. Blood pressure.
Sp. gr. Specific gravity.
R.B.C. Red blood cells.
G.F.R. Glomerular filtration rate.

ON PATIENTS WITH ACUTE GLOMERULONEPHRITIS

TM_{PAH} MG./MIN./ 1.73 SQ. M.	F.F.	G.F.R./ TM	R.P.F. /TM	RANGE OF U.F. C.C./ MIN./1.73 SQ. M.	B.U.N. MG./ 100 C.C.	REMARKS
			10.8	0.28-0.42	61	Poor test, only approximate value. Had B.P. 160/110 on 9th day.
82	0.124	0.74		1.05-3.28		Poor test, only approximate value.
25	0.084	1.76	20.9	2.54-4.61	15	
59	0.143	1.93	13.5		25.2	
85	0.115	1.19	10.4	3.26-4.88	9.9	Some doubt whether this patient had glomerulonephritis or sulfonamide intoxication. Finally decided she had both. Addis count abnormal for 5 mo., normal after 11 mo. Sed. rate never below 20 (lowest: 23 after 3 mo.)
79	0.100	1.25	12.5	2.83-4.72	13.3	
47	0.075	1.04	14.0	2.02-3.17	22.1	No follow-up.
48	0.109	1.90	17.5		19.8	
57.5	0.047	0.70	14.7	2.98-4.55	58.2	
80	0.104	0.96	9.3	3.42-4.75	18.0	
83	0.144	1.32	9.2	3.38-4.43	19.0	1.2 M. R.B.C. in Addis count 7½ mo. after onset; higher up to then. Sed. rate became normal after 6 mo.
26	0.174	4.83	27.8	4.67-6.23	10.6	
49	0.160	2.67	16.7	2.52-3.58	14.0	No follow-up.
78	0.093	0.91	9.8	2.01-3.73	14.1	
78	0.121	0.97	8.1	2.81-4.62	22.5	
101	0.115	0.88	7.65	3.20-4.44	13.9	Addis count abnormal for 6 mo., normal after 7 and 8 mo.
70	0.112	0.70	6.3	0.87-2.54	43.5	No follow-up.
	0.087			3.42-5.57	21	
				2.95-4.64		
103	0.150	1.34	8.9	1.97-2.5		
	0.115			2.15-3.54	14.8	
84	0.170	0.80	4.7	1.71-3.00		
102	0.144	0.80	5.6	1.92-4.26	12.9	B.P. was 160/90 3 days earlier, with heart failure.
108	0.150	1.09	7.3	0.94-2.44	13.7	Myocarditis. Addis count normal after 2 mo.
	0.083†			1.34-3.32		
68	0.187	1.5	8.0	2.54-4.35		
39	0.159	2.58	16.2	1.69-2.38	18.1	No follow-up.
				1.50-2.46		Had alb., many R.B.C., and hypertension 7 days previously.
30	0.079	1.60	20.4	1.24-2.45	19.5	Postscarlet nephritis, moderately severe.
84	0.124	1.01	8.2	3.11-4.20	12.8	Addis count continued showing 2-4 M. R.B.C.
76	0.159	0.84	9.5	2.93-4.72	8.6	and many W.B.C. for a year, but child had chronic vaginitis. Sed. rate normal after 4 mo.
22	0.170	2.93	17.3	1.67-2.30	12.3	
35	0.206	3.3	15.8	3.30-6.79	17.5	Sp. gr. in urine always low. No follow-up.
17	<0.254	7.3	28.7	2.11-3.03	12.6	Sed. rate became normal after 4 mo. Addis count abnormal for 6 mo., normal after 8 mo., Sp. gr. almost always low, except on the day of the test, even during Addis counts 2-10 mo. later (1017, 1023, 1013), only once 1029.
32	0.139	1.78	12.8	3.2-10.0		
56	0.187	1.6	8.5	2.57-5.12		

Urea Cl. Maximal urea clearance.
R.P.F. Effective renal plasma flow.
T_{mPAH} Maximal tubular excretory capacity for para-aminohippurate.
F.F. Filtration fraction.
U.F. Urine flow.
B.U.N. Blood urea nitrogen.

TABLE

NAME & SEX	AGE (YR.)	DAY OF ILLNESS	B. P.	EDEMA	SED. RATE MM./HR.	URINE			G.F.R.	UREA CL.	R.P.F.
						SP. GR.	ALB.	R.B.C.	C.C./MIN./1.73 SQ.M.		
20. F. G. ♂	15½	15	130/60	0	15	1019	0	1-2/hpf	87	53	1063
		29	132/80	0	23	1022	0	3-8/hpf	127	72	1027
21. K. M. ♀	6	15+	90/60	0	24	1014	1+	8-10/hpf	65	39	620
		45+	110/70	0	21	1026	0	1.283 M/12 h.	93	52	721
22. R. Su. ♂	9¾	16	140/90	0	50	1025	4+	Loaded	63 (I)	40	596
23. A. S. ♀	10	16	127/85	Trace	28	1018	Trace	40-50/hpf	84		625
		71	115/60	0	20	1030	0	1.1 M/12 h.	65		520
24. R. Z. ♂	3½	17	110/72	0		1020	2+	Few	98	73	534
25. M. McK. ♀	9	18?	110/70	0		1026	Trace	10-15/hpf	97	58	1034
26. A. P. ♂	9½	18?	115/65	0	38	1017	1+	1-4/hpf	103	71	1053
27. J. Y. ♀	7	19	110/74	0		1006	4+	50-60/hpf	27	18	>174
28. L. S. ♂	8	19	152/110	3+		1014	4+	20-25/hpf	13	8	
29. M. L. D. ♀	7½	25+	125/70	0	28	1010	4+	Few	55	34	534
		77+?	120/66	0	58		0	0-2/hpf	67	44	647
		370+?	112/78	0	24	1020	0	661,000/12 h.	118.5	66	552
30. H. R. ♂	12¹¹½	34?	106/72	0	55	1010	±	2-3/hpf	63	43	653
		58?	128/60	0	39		0	0	97	52	910
Mean value in normal children 1 to 12 years of age									130.2		611
Standard deviation.									25.3		131.5

II). Only one patient during the entire period of observation reached a G.F.R. which was above the normal mean. It is interesting that the child with the lowest G.F.R., 4 c.c. per minute (Case 1), subsequently recovered, even though his G.F.R. was only 61 c.c. per minute after six months.

Fig. 2 shows the correlation of urea clearance to glomerular filtration rate. The values fall closely around the line representing the normal ratio. The values are too irregular to allow an estimation of the G.F.R. from the urea clearance determinations. It must be noted that these urea clearance values were observed during osmotic diuresis, and may, therefore, be higher than under average conditions.

The effective renal plasma flow was usually normal, or even high, at all stages of the disease studied. The mean value for R.P.F. during the first nineteen days was 696 c.c./min./1.73 sq. M (normal mean value 611) (see Table II). The mean value for R.P.F. between the twentieth and eighty-ninth day was 699.8. The difference between the mean value of the R.P.F. in these nephritic patients and that of normal children is not statistically significant. The values recorded here for effective renal plasma flow may be lower than the true value for renal plasma flow, since Bradley and his associates[6] have demonstrated a re-

I—CONT'D

TM_{PAH} MG./MIN./ 1.73 SQ. M.	F.F.	G.F.R./ TM	R.P.F./ TM	RANGE OF U.F. C.C./ MIN./1.73 SQ. M.	B.U.N. MG./ 100 C.C.	REMARKS
80	0.082	1.09	13.2	3.39-6.40	35.4	Patient had much higher B.P., heart failure, edema, and massive hematuria before test was done. Highest NPN 69, diuresis always good; sed. rate never above 23.
86	0.124	1.48	11.9	2.86-5.17	18.8	
91	0.104	0.71	6.8	3.05-5.60	36.2	Mild heart failure. Addis count 1.6 M after 6 mo., higher before that.
83.5	0.129	1.11	8.6	2.47-3.01	10.9	Addis count sl. elevated for another mo., normal after 3-4 mo., sed. rate normal after 5 mo.
45	0.106	1.40	13.2	0.73-4.93	19.3	Routine urine normal; sed. rate still 46 after 3 wk., no further follow-up.
85	0.134	0.99	7.4	1.08-4.15	9.2	
96	0.125	0.68	5.4	1.89-4.95	12.1	
30	0.183	3.27	17.8	2.50-4.43	13.4	No follow-up.
89	0.096	1.09	11.6	1.30-1.93	20.4	
124	0.098	0.83	8.5	1.39-2.27	15.3	Scarlet fever. Addis count still 7.7 M. R.B.C. after 3 mo., not followed thereafter. Sed rate normal after 3 mo.
6.3	<0.155	4.3	27.6	1.89-5.02	43.7	Very severe nephritis with purpura. Plasma flow uncertain because Tm so low that load too high. Urine still grossly abnormal after 1 mo. No further follow-up.
0				1.13-2.24	62.2	Patient developed anuria 24th day and died 30th day. No autopsy.
31	0.103	1.77	17.2	3.34-4.12	36.3	The diagnosis in this patient was never definitely established. She was first thought to have chronic nephritis plus severe hemolytic anemia. Addis count became normal in 6 mo. Sed. rate never normal (frequent tonsillitis).
97.5	0.104	0.69	6.6	2.03-3.74	18.7	
80	0.215	1.48	6.9	2.49-3.59	14.1	
38.5	0.097	1.64	17.0	2.61-4.17	24.8	Addis count abnormal for 5 mo., normal after 9 mo. Sed. rate normal after 3 mo.
67.5	0.110	1.44	13.5	2.87-5.05	12.4	
78.3	0.213	1.92	9.44			From data obtained in the authors' laboratory.[9]
18.0	0.042	0.76	2.56			

duction in renal extraction of PAH in some cases of acute glomerulonephritis.

The F.F. was reduced in all cases except one (Case 18) and this patient also had a normal G.F.R. The mean value for the F.F. during the first nineteen days of the disease was 0.119. Between the twentieth and eighty-ninth day the mean value was 0.134. The difference between these two periods is not significant but both values are significantly lower than the normal mean value (see Table II). The four patients (Cases 7, 17, 18, 24) with the highest F.F.'s in the group had considerably reduced Tm_{PAH}. The extraction of PAH in these patients may have been sufficiently reduced to give falsely low plasma flow values resulting in falsely high F.F.'s. This also may be the case in patient 27, who had a Tm_{PAH} of 6 mg. per minute. The F.F. tended to remain low over the entire period of observation. However, with four exceptions, in the individual case there was a tendency to rise in subsequent tests (Fig. 3).

The Tm_{PAH} in many of the patients was normal throughout the course of the disease, in contrast to the G.F.R. and F.F. which were low in all but two cases (Fig. 4). However, in about half the patients the Tm_{PAH} was considerably reduced so that the mean value during the first nineteen days of the disease, 54 mg./min./1.73 sq.

TABLE II. STATISTICAL DATA ON VALUES OF RENAL FUNCTION MEASUREMENTS

	G.F.R. C.C./MIN./1.73 SQ.M.		F.F.		R.P.F. C.C./MIN./1.73 SQ.M.		$\frac{R.P.F.}{TM_{PAH}}$		TM_{PAH} MG./MIN./1.73 SQ.M.		$\frac{G.F.R.}{TM_{PAH}}$	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
I. Normal children 1-12 yr. old[9]	130.2 ± 4.96	25.3	0.213 ± 0.0078	0.042	611 ± 25.8	131.5	9.44 ± 0.48	2.56	78.3 ± 3.60	18.0	1.33 ± 0.140	0.76
II. Patients with G.N. 1st-19th day.	72.2 ± 5.69	31.2	0.119 ± 0.0085	0.043	696 ± 38.6	193.1	14.35 ± 1.26	6.04	54.3 ± 6.34	31.7	1.92 ± 0.144 1.98 ± 0.320	1.57
III. Patients with G.N. 20th-89th day.	90.5 ± 5.51	24.0	0.134 ± 0.0069	0.029	700 ± 36.7	155.8	10.05 ± 0.90	3.83	76.8 ± 5.30	22.5		0.60
IV. Patients with G.N. 90th-370th day.	96.0		0.171 ± 0.0175	0.035	661		8.92		73.5		1.16	
Difference between means of Groups I and II.	*58.0*		*0.094*		85		*4.91*		*24.0*		0.062	
S.E. of this difference	7.55		0.0114		45.8		1.36		7.29			
Difference between means of Groups I and III.	*39.7*		*0.079*		89		0.61		1.5		*0.594*	
S.E. of this difference.	7.41		0.0103				1.04				0.201	
Difference between means of Groups II and III.	*18.3*		0.015		3.5		*4.3*		*22.5*		0.656	
S.E. of this difference.	7.89		0.0110				1.55		8.27		0.350	

Notes: (1) There were only four patients in Group IV.
(2) Statistically significant differences between means are in italics.
(3) In cases where Tm_{PAH} was below 10 mg./min./1.73 sq.M., the values for F.F., R.P.F., and R.P.F/Tm_{PAH} were omitted from the calculation of statistical data.

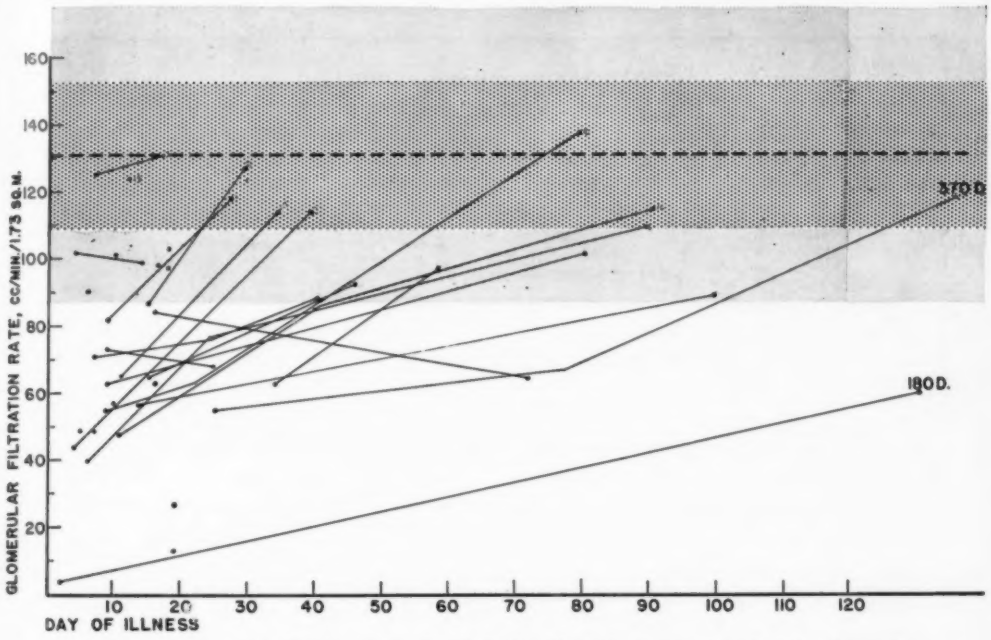

Fig. 1.—Glomerular filtration rate of indivdual patients in the course of acute glomerulonephritis. The heavy interrupted line represents the mean value in a group of normal children 1 to 12 years of age.[9] The heavily dotted zone represens ± 1 S.D. from the mean, and the light gray zone ± 2 S.D. of the mean.

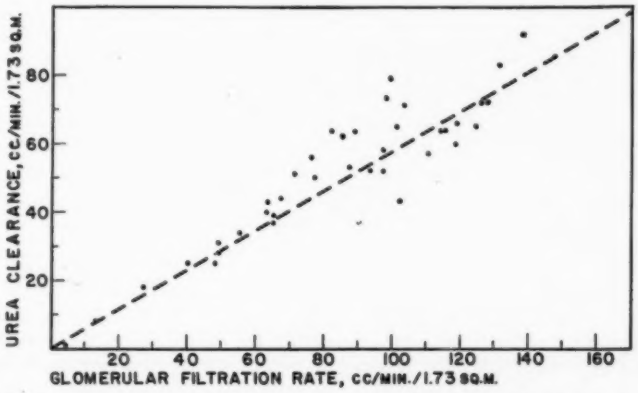

Fig. 2.—Urea clearance (C_M) plotted against glomerular filtration rate in individual patients in the course of acute glomerulonephritis. The heavy interrupted line represents the ratio of 75/130, i.e., the usual relation of normal values.

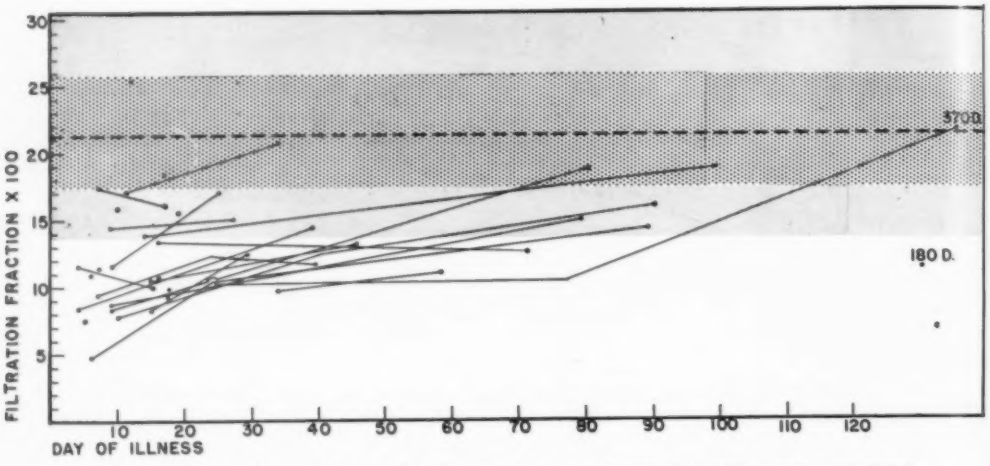

Fig. 3.—Filtration fraction in individual patients in the course of acute glomerulonephritis. The heavy interrupted line and the two zones have the same meaning as in Fig. 1.

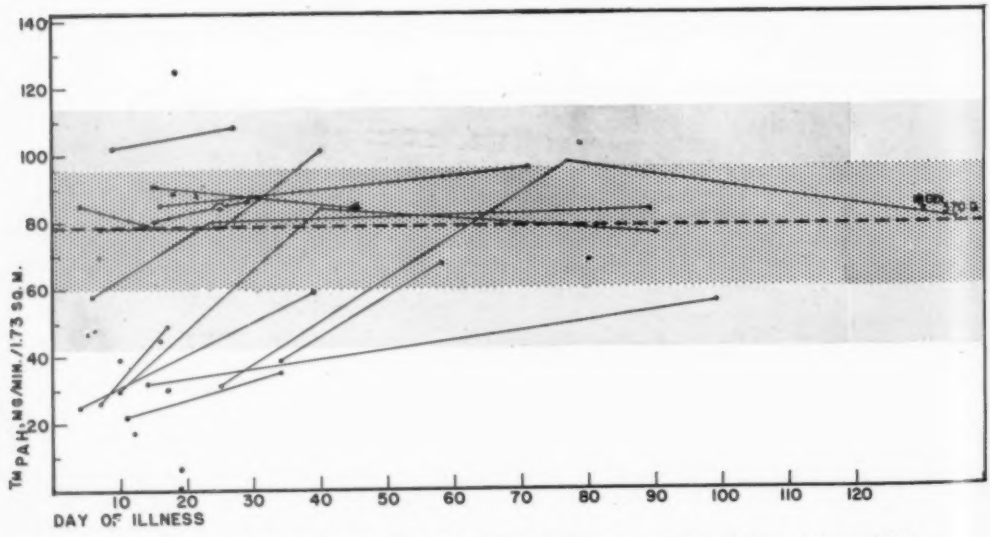

Fig. 4.—T_{mPAH} in individual patients in the course of acute glomerulonephritis. Interpretation of heavy line and the shaded zones as in Fig. 1.

M, is significantly lower than in a group of normal children. After the twentieth day, the mean Tm_{PAH} is 76.8 mg./min./1.73 sq. M, which is not significantly different from the normal value (see Table II). Two patients had extreme reduction of Tm_{PAH}, 6 and 0 mg. per minute, respectively. The child with the zero value subsequently developed anuria and died in uremia. In all instances where a subsequent test was performed in children who had had reduced Tm_{PAH} the second values were higher than the original values. Thirty-five days after the onset of the disease the Tm_{PAH} values were normally distributed. In three patients (Cases 7, 18, 24) there was a considerable reduction in Tm_{PAH} while the G.F.R. remained within the normal range. Thus, as measured by these functional tests, there was greater impairment of tubular capacity than glomerular function in these three children.

The G.F.R./Tm_{PAH} ratio was usually reduced. In the cases with normal G.F.R. mentioned above the G.F.R./Tm_{PAH} ratio was elevated.

With reduction in Tm_{PAH} in some of these patients, it might be suspected that other tubular functions are also depressed. Even though our studies were not designed to test the kidney capacity for osmotic work, data based on calculation of osmotic load (represented by mannitol plus urea alone) seem to indicate higher urine flows in the nephritic patient than in normal children at comparative loads.

The specific gravity of the urine as recorded in Table I cannot be used as a measure of renal tubular function, since it was not determined under control conditions.

The R.P.F./Tm_{PAH} ratio is an indication of the rate of perfusion of the functioning tubular tissue. A high ratio is regarded as evidence of hyperemia, and a low ratio, of ischemia.[8] As noted above, the R.P.F. values recorded here may be falsely low, due to variable degrees of reduction in PAH extraction. In such instances there would result a falsely low R.P.F./Tm_{PAH} ratio. The mean value for R.P.F./Tm_{PAH} for the first nineteen days was 14.35. This value is significantly higher than in normal children (mean 9.44). Between the twentieth and eighty-ninth day the mean value was 10.4. This value is not significantly different from the normal (see Table II). It appears that hyperemia is related to the degree of tubular dysfunction as measured by Tm_{PAH}. As seen in Fig. 5, when the Tm_{PAH} was above 60 mg. per minute, the distribution of the ratio values was normal. When the Tm_{PAH} was below 60 mg. per minute, the values, with one exception, were high. Similar observations were made by Corcoran and associates[5] who pointed out that in these cases with reduced tubular excretory function, "vicarious clearance" of PAH by diffusion of interstitial fluid from nonfunctioning to functioning tubules might explain the high R.P.F./Tm_{PAH} ratio, which only simulates hyperemia of functioning tissue. However, true hyperemia has been observed in this essentially inflammatory disease. The over-all data do not indicate the existence of ischemia at any stage. This finding is in agreement with the observa-

tions of Bradley and collaborators[6] who have recorded true values for R.P.F. by correcting Tm_{PAH} clearances for the observed PAH extraction ratios.

In order to determine whether the functional pattern, as expressed by these specific tests, parallels the clinical expression of the disease, certain of the common clinical features are correlated with functional measurements.

Hypertension was noted in eight of sixteen patients studied during the first ten days of their disease. There was no obvious difference in R.P.F. values between the hypertensive patients and those with normal blood pressures. However, in three of the hypertensive patients the renal plasma flow rose significantly with recovery from the disease. In the other five there was no significant change in R.P.F. When the existence of hypertension is correlated with the R.P.F./Tm_{PAH} ratio there is likewise no evidence that renal ischemia is present during the hypertensive phase. The rise in R.P.F. seen in the three patients after recovery from hypertension may be spurious and result from improvement in the extraction ratio for PAH. The possibility of vasospasm being a factor in the reduced renal plasma flow of the above three patients must be considered, but it is obviously not a regular feature in hypertension of acute glomerulonephritis.

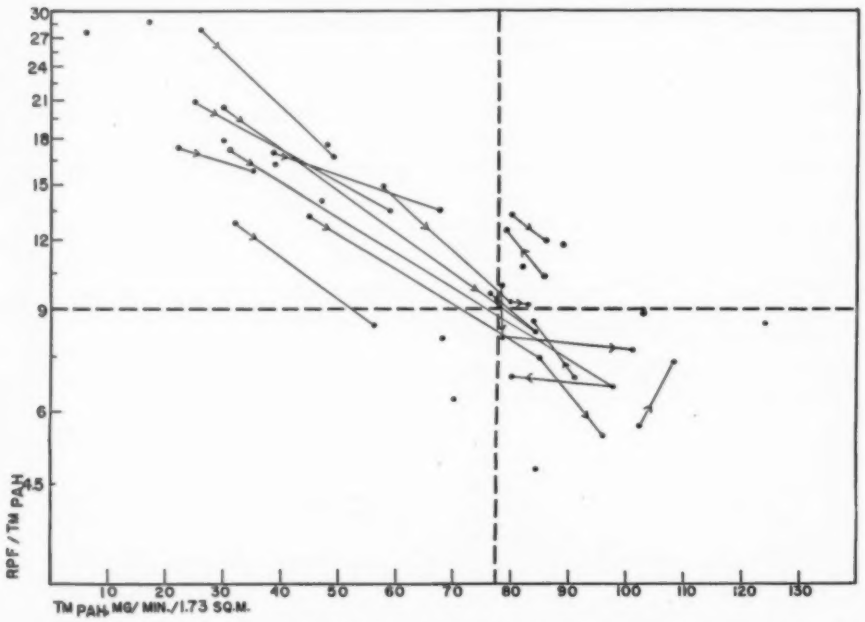

Fig. 5.—R.P.F./Tm_{PAH} ratio plotted against simultaneously observed Tm_{PAH}. The values obtained in consecutive tests on the same patient are connected by thin lines with the arrows indicating the sequence of observations.

The mean G.F.R. in patients with hypertension was about the same as in the nonhypertensive group studied in the first ten days of the disease. The F.F. was equally reduced in both groups of patients unlike that seen in essential hypertension and offering no clue to a correlation between glomerular dysfunction and hypertension.

Of the sixteen patients studied during the first ten days of the disease, nine had clinical edema. The G.F.R. in these patients was not significantly different from that in the nonedematous patients studied in the corresponding period. Furthermore, the studies of Earle and associates[7] suggest that the converse to water retention, diuresis, may be more closely related to changes in tubular function (water reabsorption) than to changes in G.F.R.

In eight cases (3, 11, 13, 15, 19, 21, 23, and 30) clearance studies were made after albumin and red blood cells had disappeared from the urine, ten to ninety-nine days after onset of disease. In four of these, the urinary sediment was also examined by the Addis count technique. Where sedimentation rates were determined they were still rapid. The values for G.F.R. at this time were all still reduced, three of them considerably so. The F.F. was still significantly reduced in four of seven patients at this stage.

Nasopharyngeal cultures were taken at the time of admission to the hospital. Thirteen of the patients showed predominance of *Staphylococcus aureus* (three of these associated with pneumococci) and twelve had a predominance of Beta hemolytic streptococci. There was no significant difference in the G.F.R. of these two groups studied in the first ten days of the disease. Twenty of these patients received penicillin therapy, and two were treated with sulfonamides. There were too few patients untreated to draw comparison of the rate of recovery in renal function between treated and untreated patients.

SUMMARY

1. Acute glomerulonephritis results in disruption of the renal functional pattern. G.F.R. and F.F. are significantly reduced in the early stages of the disease, with few exceptions, and may remain so for several months, often after albumin and red blood cells have disappeared from the urine.

2. Functioning tubular mass, as measured by Tm_{PAH}, is considerably reduced in about half the patients. In an occasional patient with significantly reduced Tm_{PAH} the G.F.R. remains within normal limits, indicating a greater degree of tubular than glomerular dysfunction.

3. Hyperemia of the kidney tissue as measured by the $R.P.F./Tm_{PAH}$ ratio was observed in those cases with a significantly reduced Tm_{PAH}. Ischemia of the kidney tissue as measured by a low value of the above ratio is not a part of the pattern of acute glomerulonephritis. It, therefore, does not appear to be a factor in the hypertension noted in half of our patients studied early in their disease.

4. With clinical recovery there is a return toward normal of renal function as measured by the tests

used. Functional recovery is frequently delayed beyond clinical recovery.

REFERENCES

1. Rubin, M. I.: Studies on Renal Function in Childhood, Pennsylvania M. J. **51**: 617, 1948.
2. Hilden, T.: Diodrast Clearance in Acute Nephritis, Acta Med. Scandinav. **116**: 1, 1943.
3. Earle, D. P., Jr., Taggart, J. V., and Shannon, J. A.: Glomerulonephritis. A Survey of the Functional Organization of the Kidney in Various Stages of Diffuse Glomerulonephritis, J. Clin. Investigation **23**: 119, 1944.
4. Hilden, T.: Diodrast Clearance in Acute and Chronic Glomerulonephritis, Acta Med. Scandinav. supp. **206**: 246, 1948.
5. Corcoran, A. C., Taylor, R. D., and Page, I. H.: Functional Patterns in Renal Disease, Ann. Int. Med. **28**: 560, 1948.
6. Bradley, S. E., Bradley, G. P., Tyson, C. J., Curry, J. J., and Blake, W. D.: Renal Function in Renal Disease, Am. J. Med. **9**: 766, 1950.
7. Earle, D. P., Farber, S. J., Alexander, J. D., and Pellegrino, E. D.: Renal Function and Electrolyte Metabolism in Acute Glomerulonephritis, J. Clin. Investigation **30**: 421, 1951.
8. Smith, H. W.: The Kidney. Structure and Function in Health and Disease, New York, 1951, Oxford University Press.
9. Rubin, M. I., Bruck, E., and Rapoport, M.: Maturation of Renal Function in Childhood: Clearance Studies, J. Clin. Investigation **28**: 1144, 1949.

SOME COMMENTS ON HERPETIC INFECTION IN CHILDREN WITH SPECIAL EMPHASIS ON UNUSUAL CLINICAL MANIFESTATIONS

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SOME EPIDEMIOLOGIC CONSIDERATIONS

THE virus of herpes simplex is considered to be one of man's oldest parasites.[1] As a result most infections by this virus are inapparent and, although the virus is ubiquitous in man's environment, we, as physicians, encounter clinical cases of serious herpetic infection relatively rarely. Among adults, and to a lesser extent among children, recurrent herpes of the lips and face is, of course, a common and annoying although not a serious disease. However, it is largely among children that we do find patients suffering serious illness as the result of their first contact with this virus.

Since the observations of Burnet and Williams[2] in 1939 it has been clearly recognized that herpetic infection in man presents itself in two forms: (a) a primary infection which occurs in persons without the presence of circulating antibody and which, when it does cause clinical manifestations, is likely to give rise to a clearly recognizable systemic illness in addition to local lesions at various sites; (b) a recurrent infection which occurs in carriers who have neutralizing antibodies in their blood at the time of the recurrence. Such recurrent lesions do not as a rule cause any systemic illness, but only local collections of vesicles. Serologic surveys[3, 4] for the presence of neutralizing antibodies have shown that the incidence of infection is widespread, although higher among the lower socioeconomic groups, but little has been done to elucidate the relative incidence of clinical disease to the incidence of primary infection.

In 1948 there was a brief report[5] from this laboratory on a study of patients attending the outpatient clinic of the Children's Hospital of Philadelphia, which is situated in one of the lower socioeconomic sections of the city. In order to obtain an approximate quantitation of the relative incidence of clinical and inapparent primary infections we were called to see all cases of acute herpetic gingivostomatitis during an eight-month period. We found that there were thirty-eight cases of herpetic gingivostomatitis among 5,016 patients under the age of 5 years. However, by that age among the same population, 60 per cent had been infected by the herpes virus as shown by the presence of neutralizing antibodies. Among accompanying adults the incidence of circulating antibodies was 63 per cent. This meant that less than 0.8 per cent of herpetic infections caused clinical manifestations.

A more accurate accounting of the incidence of clinical herpetic stomatitis among a carefully supervised group of 1,000 families of variable socioeconomic status has been carried out by Spence, Court, and Miller,[6] in Newcastle, England. Their cumulative

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These studies were conducted under a grant-in-aid from the United States Public Health Service.

figures for the incidence of stomatitis during the first 5 years are eighty-five cases out of 950 children observed (9 per cent). Therefore even with the most careful observation the relative rarity of clinical herpes is striking when compared with a total incidence of herpetic infection. Some caution must be taken over a generalization of this sort, however, since under special circumstances, such as the inevitable increased crowding of an institution, an incidence of over-all infection of 100 per cent and clinical stomatitis of 55 per cent have been described by Anderson and Hamilton[7] among thirty-six susceptibles in an orphanage in Melbourne, Australia.

Since it is a matter of general experience that herpetic gingivostomatitis rarely occurs before 1 year of age, it is of interest to examine the time relationships of antibody formation in this infection. Anderson and Hamilton[7] reported that they could not detect transmitted maternal antibodies after 6 months although their earliest infection was at 11 months. Among our clinic patients the percentage of persons with antibody dropped to a very low level between 4 months and 2 years but had reached adult level by 5 years. (Fig. 1.) Although cases of primary infection are reported as young as 5 months[8] the relative resistance of children between 6 months and 1 year requires explanation.

Following the primary infection circulating neutralizing antibodies against the virus appear in the blood often as early as the fourth day of illness, and rise steeply (Fig. 2). This means that for diagnostic purposes blood should be drawn from the patient on the first visit. With the development of antibodies the patient recovers and there is considerable evidence in favor of the hypothesis that the virus then becomes latent for the rest of life, and by constant stimulation keeps the level of antibodies at a constant level. This hypothesis is supported by our experience with a limited number of adults in whom, regardless of frequency of attack, the level of antibodies against a standard strain of herpes remained approximately constant for months in a given

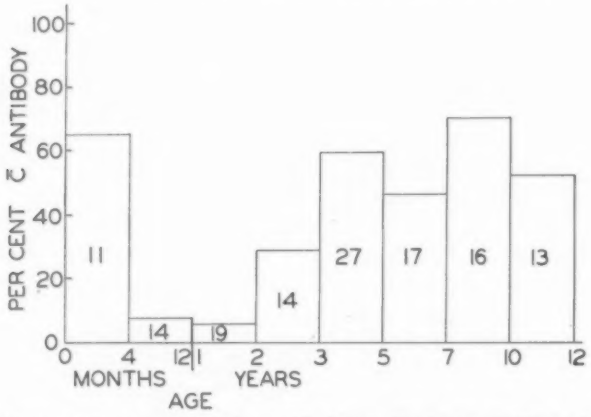

Fig. 1.—Incidence of herpes neutralizing antibodies in the blood of 131 children. Numbers in each box indicate number of children tested at each age group.

individual (Fig. 3). Jawetz and Coleman[9] in a more intensive study using a different technique also found the same to hold for six of eleven patients studied. However, from their reported tables, it appeared that in two children, following the healing of active herpetic keratitis, there was a persistent fall of antibodies during the subsequent months. Furthermore, in three other patients, one child and two adults, there were fluctuations in titer beyond those expected from experimental error. Complete disappearance of antibody from the blood of a 20-month-old infant, seven to nine months after an attack of Kaposi's varicelliform eruption (eczema herpeticum) has been noted by Wenner.[8] These exceptions raise the question as to

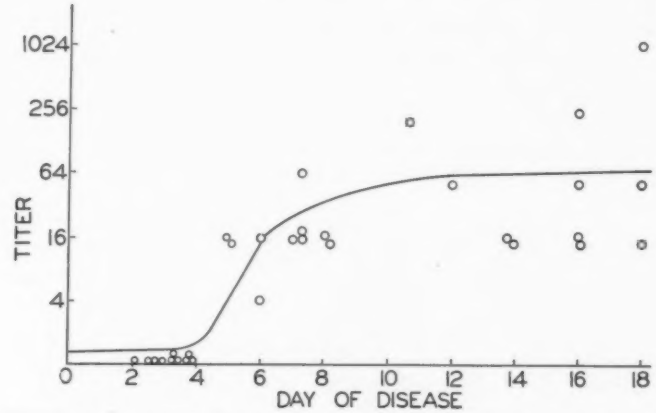

Fig. 2.—Levels of herpes neutralizing antibody in thirty-one children at different periods after the onset of their primary infection.

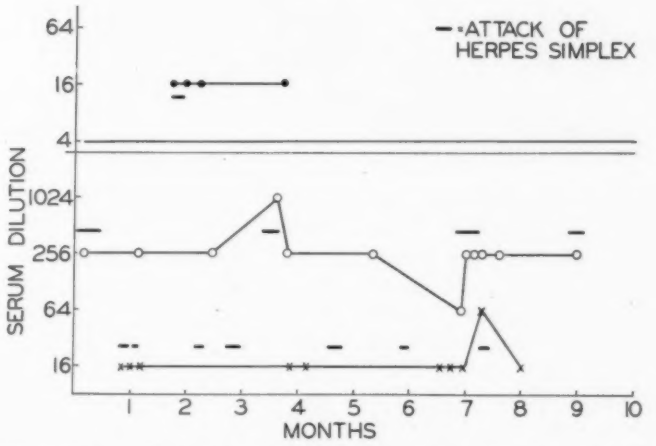

Fig. 3.—Neutralizing antibody level in three adults with recurrent attacks of herpes simplex.

whether the development of a latent virus and consequent antibody stimulation may always occur after one attack or whether, in some individuals at least, antibody titers depend on repeated reinfections.

DIAGNOSIS

Before turning to a description of some of the less common clinical manifestations of the primary infection which may not at first be recognized as herpetic, a short reminder about diagnostic procedures may be in order.

1. *Serologic methods.* It is well recognized now that the diagnosis of the majority of viral diseases[10] can be confirmed in the laboratory only when the patient has had time to develop antibodies, so that a comparison can be made between the titer of antibodies in the acute and convalescent sera. Herpetic infection is no exception to this rule, hence the importance of an early blood specimen. This technique is the only one by which a differential diagnosis between a primary and recurrent attack can be made. However, it cannot provide a rapid diagnosis of an herpetic lesion in a given patient.

2. *Isolation of virus.* Another confirming laboratory procedure, from which an answer can be obtained somewhat sooner, is that of the isolation of the herpes virus. This is relatively easy in a properly equipped laboratory.[11] However, virus can only be obtained from fresh and not from purulent vesicles. This does not apply to isolation of virus from patients with stomatitis since virus is shed into the saliva whence it can be isolated for a relatively long time.

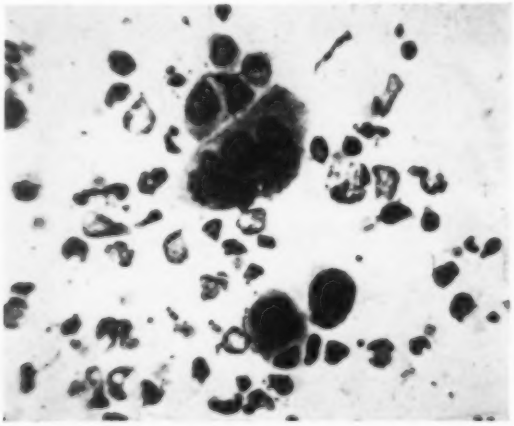

Fig. 4.—Virus giant cells from the scrapings of fresh vesicle, stained with Giemsa.

3. *Cytologic.* This is much more applicable to immediate diagnosis and should be widely used. Following the observations of Tzanck,[12] Blank and associates[13] have described a technique whereby characteristic giant cells can be observed in scrapings from the base of a fresh vesicle stained with fresh Giemsa (Fig. 4). These cells occur only in herpes simplex, herpes zoster, and varicella, so that the differential diagnosis of vesicular lesions is markedly reduced.

CLINICAL MANIFESTATIONS

The usual designation of the herpes virus as being primarily ectodermotropic with the consequent convenient clinical classification of diseases of the skin, mucous membranes, eye, and central nervous system cannot now be held as providing a complete description. The recent reports[14, 15] of fatal neonatal infection in full-term and premature infants with involvement of internal organs especially the liver and lungs demonstrate clearly the presence of viremia and the pantropic potentialities of the virus. The relative role of viremia in primary infection requires further investigation. Ruchman and Dodd[16] reported the isolation of virus from the blood of a patient with primary nasal infection, while Dudgeon[17] found virus in the blood of two severely ill patients with eczema herpeticum but failed to find it in three others who suffered mild attacks of the same disease. We have isolated virus from the blood of one patient with severe eczema herpeticum but failed in seven other attempts from primary infections of various types.

UNUSUAL MANIFESTATIONS OF PRIMARY INFECTION OF MUCOUS MEMBRANES, SKIN, AND CENTRAL NERVOUS SYSTEM

Herpetic Vulvovaginitis

The occurrence of both recurrent and primary vulval herpes is recognized in adults[18]; it is rare in children.[18a] Three primary infections among Negro children of 18 months, 12 and 13 years of age have been seen in the last six years with a characteristic clinical picture illustrated by one of them.

I. D., a 12-year-old Negro girl, was seen in the clinic on Nov. 15, 1950, with the complaint of "boils about her privates." Four days previously her vulva had become uncomfortable and this discomfort had grown steadily worse. "Boils" had been noticed on the previous evening when she had had fever and pain on urination. On examination the child had an oral temperature of 100° F. On the labia majora many grayish vesicles were seen which were foul smelling. Pain, requiring aspirin for relief, delayed her sleep that night. On the next day her temperature was 98° F. and both labia majora and minora showed no fresh vesicles but numerous yellow ulcers 2 to 4 mm. in diameter, each with red areola which were moderately tender (Fig. 5). The inguinal lymph nodes were enlarged to hazelnut size bilaterally and were also tender. With sitz baths and intramuscular procaine penicillin her lesions were practically healed by the tenth day after onset.

Fig. 5.—Primary herpetic vulvovaginitis. Note the similarity of the lesions to those of herpetic gingivostomatitis.

Laboratory Studies: In the absence of fresh vesicles it was not surprising that no virus was isolated nor characteristic cells seen in smears taken from the lesions on November 16. The primary nature of the attack was proved by the demonstration of a marked rise both in complement fixing antibodies from 1:4 to 1:32 and neu-

tralizing antibodies from 1:32 to > 1:256 between the fifth and tenth day after onset.

This patient was of especial interest because in her history we found that at the age of 2 years she had had an illness characterized by a membranous stomatitis which at that age and from the description was quite possibly of herpetic origin. However, in the intervening ten years she had had no fever blisters, although they did occur in two younger brothers, whose current attacks had provided a source of infection for her present illness. It seems possible, although unproved, that this child had actually suffered a second, clinically manifest, "primary" attack due to loss of immunity following her original stomatitis.

In one of the other patients vesicles on the adjoining skin helped to suggest the diagnosis.

Diseases of the Skin

1. *Traumatic Herpes.*—In 1938, with Findlay and MacCallum,[19] I saw my first case, a white girl of 5 years, who had recurrent attacks of a large bullous eruption of the palm of her right hand. This had started three years previously, eleven days after a gravel graze of that hand. In the last six years two similar patients have been seen at The Children's Hospital of Philadelphia.

L. H.,* a 15-month-old white infant, was seen on Dec. 21, 1950, ten days after she had burned the fourth finger of her left hand on a cigarette. Her mother at that time was suffering from a recurrent attack of "cold sores." For the first two days the burn appeared to be healing. However, on the third day the site became swollen, red, and painful. By the seventh day new blisters began appearing on other parts of the hand and arm and continued to do so for the next two days. At this time the child had a temperature of 102° F., was irritable, sleepless, and had lost her appetite—although no soreness of the mouth was noted until the day of her visit. Examination revealed an irritable but not acutely ill child with a temperature of 100° F. (R). On the palm of the left hand were two large purulent bullae contiguous to the open burned area; there were six to eight small discrete vesicles on the front of the fourth finger and back of the third and fourth fingers (Fig. 6), groups of vesicles on

Fig. 6.—Lesions of traumatic herpes, tenth day after injury, showing scattered vesicles on the palm.

the back of the same wrist and just above the medial condyle, and one vesicle on the lateral aspect of the anticubital space. All the vesicles were purulent. The left epitrochlear and left axillary nodes were enlarged. Her mouth presented the picture of mild herpetic stomatitis; the gums about the upper incisors were red and swollen and she had two blisters under her upper lip and two on the gum adjoining the first premolar. She was treated with penicillin and sulfadiazine and the skin lesions were dressed with aureomycin ointment. Her temperature remained elevated between

*Referred by Drs. T. S. Wilder and R. M. Shelley.

100 and 101° F. (R) until December 25. However, her mouth recovered quickly, and by this day the child was eating a normal diet. The skin lesions dried and scabbed quite slowly but except for the original burn were healed by Jan. 6, 1951. A recent follow-up almost two years later revealed that she had had several recurrences of groups of vesicles confined to the site of the original burn.

eruption at the site of his graze, and secondary vesicles along his upper arm with enlargement of axillary lymph nodes on the affected side which were at first diagnosed as herpes zoster (Fig. 7). Herpes simplex virus was isolated from his lesions and he developed a rise in herpes antibodies. During the year he was followed he developed recurrences on the original site four and eleven months after his

Fig. 7.—Distribution of lesions of traumatic herpes of the elbow resembling herpes zoster.

Laboratory Studies: Virus was isolated from the saliva but not from the purulent lesions of the skin. The primary nature of the attack was established by demonstrating a rise of titer of neutralizing antibodies from $< 1:4$ on Dec. 21, 1950, to 1:8 on Jan. 12, 1951.

It is of interest to point out the abortive nature of the stomatitis which appeared several days after the skin lesions and cleared in about four days. It is also worth noting that there appeared to be an incubation period of four days between the appearance of the first blister and that of the scattered ones that followed. A similar observation has been made by Dudgeon[17] in cases of eczema herpeticum.

A second case occurred in a white boy in his second year who had fallen and grazed his elbow. Both his parents had "cold sores" at the time of his injury. He developed a vesicular injury despite a high level of circulating antibody.

2. *Primary Infection in Apparently Unbroken Skin.*—

C. G.,* a 10-year-old white girl who used to have attacks of flexural atopic eczema during the summer was seen on Jan. 23, 1948, with a history of a slightly pruritic lesion on her right temporomandibular region of four days' duration. The lesion had gradually grown larger but there had been no fever or malaise. On examination there was a 3 cm. lesion consisting of a red edematous base covered with confluent 2 to 4 mm. vesicles and some crusts. It had been treated with gentian violet by the mother. The preauricular lymph node was enlarged and slightly tender on that side. No other nodes were enlarged. The diagnosis was made by finding a significant

*A patient of Dr. Donald Pillsbury, Department of Dermatology, School of Medicine, University of Pennsylvania.

rise of neutralizing antibodies against herpes between Jan. 23 and Feb. 18, 1948. Although there were minimal residual lesions of atopic eczema in the flexures of her limbs, her face was clear.

Herpetic Encephalitis

This entity has been recognized since 1941[20] but almost all the reported cases have been fatal. Recently Afzelius-Alm[21] has reported that this virus may be the cause of more cases of encephalitis with recovery than has been generally recognized. The following appears to be such a case.

N. P., a 4-year-old white boy was admitted to the Neuro-Surgical Service* of the Children's Hospital of Philadelphia on Oct. 15, 1950, as a possible case of posterior fossa tumor or brain abscess. Two days before admission he had fallen down fifteen steps without obvious injury. On the evening of the following day he had become irritable and feverish. On the morning of admission he had vomited and in the afternoon had had a convulsion followed by increasing stupor. On admission the boy's temperature was 99° F. (R), pulse 78, respiration 44, blood pressure 76/54, and his weight was 23 pounds. He was semistuporous, being aroused only by painful stimuli. His neck was moderately stiff and he cried when his head was flexed. MacEwen's sign was markedly positive. His pupils were of normal size and reacted to light. Corneal reflexes were diminished. Fundoscopic examination showed venous engorgement and slight papilledema of 1 to 2 diopters and multiple small hemorrhages bilaterally with one prehyaloid hemorrhage at the upper pole of the right disc. There was general weakness of all extremities but no localizing signs. Deep tendon reflexes were all hypoactive to absent. Kernig's sign was present bilaterally and Babinski's sign was positive on the left. In his mouth probable early herpetic lesions were described as purulent material on the right tonsil with pharyngeal lymphoid hyperplasia.

Laboratory Findings: On October 16 hemoglobin was 10.9, white blood count 31,150, polymorphonuclears 76, lymphocytes 21, eosinophils 3. Urinalysis was negative. Ventriculogram was normal. On October 18 the cerebral spinal fluid was clear, white blood count 370, 42 per cent polymorphonuclears, 58 per cent mononuclears. Pressure was 140 cm. H_2O. On October 20 an electroencephalogram showed cerebral arrhythmia with bizarre wave forms and abnormal slow frequency.

TABLE I

DAY OF ILLNESS	NEUTRALIZING ANTIBODIES	COMPLEMENT FIXING ANTIBODIES
5th	1:4	1:2
9th	1:32	1:16
14th	1:512	1:32

Course: Ventricle and subdural taps on admission revealed clear fluid from left ventricle under a pressure of 400 mm. H_2O, clear subdural spaces, and no fluid from right ventricle. He had one convulsion and vomited extensively following the ventriculogram. Because of vomiting and refusal to take fluids he was maintained by intravenous fluids, blood, and gavage feedings until October 21. Otherwise he was treated with sedatives, aureomycin, and streptomycin. His temperature ran an irregular course, sometimes spiking to 102.5°, until October 23. His stupor slowly cleared and he was able to play with toys by October 21. His fundi on October 17 were much the same as on admission except that there were discrete white spots seen bilaterally and the picture suggested leukemia or septicemia. By

*Dr. Eugene Spitz, Chief of Service.

October 18 his mouth lesions were typical of herpetic stomatitis, and by October 21 he had herpetic lesions on the skin about his nose. Following the subsidence of fever he made a rapid recovery and was discharged on October 28 with slightly blurred discs as the sole remnant of his fundal changes and a slight left hemiparesis involving mainly the leg. Within one month this had largely disappeared and no evidence of sequelae has been noted on his several visits to the hospital during the last two years. Table I shows the antibody response against HF strain of herpes simplex.*

SUMMARY

A review of the epidemiology of herpetic infection has illustrated areas in which further information is still needed. The clinical presentations were made with the objective of drawing the attention of clinicians to some of the more unusual manifestations of this infection so that it may be considered more regularly in mucous membrane and skin lesions and encephalitis in children. The relation of maternal immunity to fatal herpetic infection of the newborn infant is a further area for investigation.

REFERENCES

1. Burnet, F. M.: Virus as Organism, Boston, 1945, Harvard University Press.
2. Burnet, F. M., and Williams, S. V.: Herpes Simplex. A New Point of View, Med. J. Australia **1**: 637, 1939.
3. Andrewes, C. H., and Carmichael, E. A.: Presence of Antibodies to Herpes Virus in Post Encephalitis and Other Human Sera, Lancet **1**: 857, 1930.
4. Burnet, F. M., and Lush, D.: Herpes Simplex Studies on the Antibody Content of Human Sera, Lancet **1**: 629, 1939.
5. Scott, T. F. McNair, Coriell, L. L., and Blank, H.: Infections With the Virus of Herpes Simplex, (Abst.) Am. J. Dis. Child. **79**: 951, 1950.
6. Spence, Sir James, Miller, F. W., and Court, D.: Personal communication from the Thousand Family Survey, Newcastle, England.
7. Anderson, S. G., and Hamilton, J.: The Epidemiology of Primary Herpes Simplex, Med. J. Australia **1**: 308, 1949.
8. Wenner, H. A.: Complications of Infantile Exzema Caused by the Virus of Herpes Simplex, Am. J. Dis. Child. **67**: 247, 1944.
9. Jawetz, E., and Coleman, V. R.: Studies on Herpes Simplex. IV. The Level of Neutralizing Antibodies in Human Sera, J. Immunol. **68**: 655, 1952.
10. Virus and Rickettsial Infections in Man, ed. 2, T. M. Rivers, ed., Philadelphia, 1952, J. B. Lippincott Co.
11. Diagnostic Procedures for Virus and Rickettsial Diseases, T. Francis, Jr., ed., Am. Pub. Health A., 1948.
12. Tzanck, A.: Le Cyto-Diagnostic immediat en Dermatologie, Ann. dermat. et syph. **7**: 68, 1947.
13. Blank, H., Burgoon, C. F., Baldridge, G. D., McCarthy, P. L., and Urbach, F.: Cytologic Smears in Diagnosis of Herpes Simplex, Herpes Zoster and Varicella, J. A. M. A. **146**: 1410, 1951.
14. Quilligan, J. J., and Wilson J. L.: Fatal Herpes Simplex Infection in a Newborn Infant, J. Lab. & Clin. Med. **38**: 742, 1951.
15. Zuelzer, W., and Stulberg, C. S.: Herpes Simplex Virus as the Cause of Fulminating Visceral Disease and Hepatitis in Infancy, Am. J. Dis. Child. **83**: 421, 1952.
16. Ruchman, I., and Dodd, K.: Recovery of Herpes Simplex Virus From the Blood of a Patient With Herpetic Rhinitis, J. Lab. & Clin. Med. **35**: 434, 1950.
17. Dudgeon, A.: The Pathogenesis of Herpes Simplex, a communication to the Pathological Section of the Royal Society of Medicine, March, 1952.
18. Slavin, H. B., and Gavette, E.: Primary Herpetic Vulvo-Vaginitis, Proc. Soc. Exper. Biol. & Med. **63**: 343, 1946.

18a. Krugman, S.: Primary Herpetic Vulvovaginitis. Report of a Case; Isolation and Identification of Herpes Simplex Virus, Pediatrics **9**: 585, 1952.

19. Findlay, G. M., and MacCallum, F. O.: Recurrent Traumatic Herpes, Lancet **1**: 259, 1940.
20. Smith, M. G., Lennette, E. H., and Reames, H. R.: Isolation of the Virus of Herpes Simplex and the Demonstration of Intranuclear Inclusion Bodies in a Case of Acute Encephalitis, Am. J. Path. **17**: 55, 1941.
21. Afzelius-Alm, L.: Aseptic Encephalomeningitides in Gothenburg, 1932-1948. Clinical and Experimental Investigation With Special Reference to the Viruses of Herpes, Influenza, Mumps and Lymphocytic Chorio-meningitis, Göteborg, 1951.

*It is realized that all criteria for diagnosis have not been fulfilled and that an encephalitis of another origin may have occurred coincidentally with a primary herpetic gingivostomatitis. However, the almost identical timing of onset of the two make a single diagnosis reasonably acceptable.

HOSPITAL CROSS-INFECTIONS AND THEIR CONTROL

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Dr. Park, painfully aware of the high incidence of cross-infection in the Harriet Lane Home, stimulated early studies of Dr. Horace Hodes on the spread of pneumococcal infections in the Harriet Lane wards. Later, foreseeing the benefits both to Pediatric Hospitals and to the Armed Forces of effective methods of cross-infection control, he invited Dr. O. H. Robertson, then director of the Army Commission on Air-borne Infection, to make use of the wards in the Harriet Lane Home for studies on glycol mists. Dr. Clayton Loosli, at the time Major in the Medical Corps, U. S. Army, was placed in charge of the investigations, which were carried out with the assistance of Dr. Margaret Smith, then Instructor in Pediatrics at Johns Hopkins.

THE problem of cross-infections in hospitals and institutions continues to be very vexing. When the sulfonamides and the antibiotics first came into general use a few years ago, it was tacitly hoped that the practical problem of nosocomial infections would be eliminated, at least in so far as bacterial infections were concerned. Increasing experience with these agents has shown that such is not the case. The widespread use of chemotherapeutic and antibiotic agents has, by decreasing the number of susceptible organisms, given free rein to less susceptible ones, with frequent appearance of gram-negative rods and of antibiotic-resistant strains of gram-positive organisms such as staphylococci and streptococci.[1-6] These then spread, giving rise to hospital and ward outbreaks of disease which are both difficult to control and extremely difficult to treat.

Careful study reveals the problem to be world wide. Hospitals in England,[7, 8] in Australia,[9, 10] and in this country[11] report outbreaks of staphylococcal disease in newborn nurseries and children's wards, many of them due to penicillin-resistant organisms.[1, 3, 4, 12] Shigella and Salmonella infections have broken out in England,[13-15] Australia,[16] and the United States.[17, 18] Enteric diseases due to less well-established pathogens such as group D streptococci,[20] newly recognized strains of colon bacilli,[21-24] have made their appearance repeatedly. Coliform bacteria have also been incriminated in outbreaks of respiratory disease in Scandinavia and the United States.[6, 25, 26] Nor have the respiratory pathogens usually associated with hospital infections been absent: hemolytic streptococci,[27-32] pneumococci,[33-35] the diphtheria bacillus[36] have all within recent years been associated with hospital outbreaks of disease. Of particular interest are reports on smouldering outbreaks of infectious hepatitis in children's nurseries,[37-39] one of which has been going on for ten years.

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In final analysis, then, the problem of nosocomial infections is far from obsolete. It is still very much with us; and the chances are that it always will be, since pathogenic microorganisms are able to produce so many generations of descendants in such a short time that a given strain can readily adapt itself to the presence of certain antibiotic substances; hence the great increase within a few years in the numbers of sulfonamide-resistant streptococci[32] and, more recently, penicillin-resistant staphylococci.[16]

Such being the case, we must see what we know about the "pathogenesis," so to speak, of cross-infections in hospitals, and take stock of current control measures.

Man's effort at controlling hospital infections has an interesting history, linked to that of his attempts at preventing epidemic diseases in general. For centuries there have existed hospitals for patients with infectious diseases such as leprosy, plague, yellow fever, typhus—institutions which had as their prime purpose the segregation of the sick from the healthy. What happened to the persons so hospitalized was apparently not a matter of public concern. This concept of the isolation hospital as simply a place of detention, effective and necessary in the control of outbreaks of infectious disease, persisted until well into the present century; in this country it was dealt a death blow by Chapin's addresses and writings between 1907 and 1921.[40] Gradually this idea of the isolation hospital as merely a protection for the public was modified under the effect, on the one hand, of the new science of bacteriology and, on the other, of the forceful growth of a sense of social responsibility.

McNeill,[41] writing in 1895 on the "Prevention of Epidemics and the Construction and Management of Isolation Hospitals," expresses this then relatively new point of view very clearly, as follows: "the primary object of providing Isolation Hospitals is . . . to *prevent infection from spreading* (McNeill's italics) by the seclusion or separation of persons suffering from infectious ailments from all who may be susceptible to catch these diseases," and again, a few pages later: "If more than one infectious disease is to be treated at one time in the hospital it is quite as important to have a safe space or sanitary zone between the wards occupied by different infectious diseases as it is to have a safe sanitary zone between the hospital and the public. Indeed it is in some respects of more importance."

Air-borne transmission of all types of infectious disease had long been generally accepted, and the experiments of Tyndall, Pasteur, and others had confirmed the presence of bacteria in the air. It was logical, therefore, that Lister's first attempts at preventing postoperative wound infections consisted in using carbolic acid air sprays. He soon learned, however, that disinfection of hands and instruments sufficed to prevent most wound infections without the use of sprays. Meanwhile Semmelweis's[42] painstaking observations, made many years earlier, became widely known and accepted. Semmelweis had shown conclusively that disinfecting the hands after dissecting cadavers and before examining patients cut down drastically on the incidence of puerperal fever; and that the disinfection of the examiner's hands *between* patients and the use of clean bed linen were equally necessary to

prevent outbreaks of disease. Lister's and Semmelweis's conclusions as to the effectiveness of aseptic techniques in the operating room and in the wards led Grancher[43] and Hutinel[44] in Paris to introduce similar measures into the wards of children's hospitals. The year 1900 marks the founding of the Pasteur Hospital in Paris, where relatively successful "barrier nursing" of patients with different infectious diseases in the same ward was carried out. This hospital soon served as a model for others of its kind in Europe. Its example was followed in 1911 by the opening of similar special facilities in the United States at the Providence City Hospital, under the leadership of Charles Chapin. Chapin's hospital served from then on as a model for infectious disease and pediatric units in this country.

Chapin himself was apparently convinced that "air infection is of no importance . . . and that contact infection can be prevented by proper technique."[40] He strongly discouraged fumigation, and emphasized soap and water, simple sterilization of instruments, etc., as the basis of control of cross-infection. The relatively simple rules which he laid down are those followed today in most carefully managed units devoted to the care of children and adults with communicable diseases.

So gratifying were at first the results of controlling contact infection that Fluegge himself, the great early student of air-borne infection, states at the end of a detailed analysis of his experimental data: "I do not doubt that far and away the greatest number of wound infections arise through *contact*" (Fluegge's italics).[45] His conclusion seemed so close to the truth that interest in air-borne infection again became dormant until aroused by the studies of Wells in the early 1930's.

Wells greatly amplified Fluegge's methodical observations; he showed that moisture droplets with adherent infectious particles may remain suspended in the air for hours.[46, 47] In the course of studying the viability of such suspended microorganisms when subjected to the action of various physical and chemical agents, Wells and Fair[48] found atomized cultures of *B. coli* particularly susceptible to ultraviolet irradiation, the germicidal properties of which were already well known. After a series of experiments on air sterilization with ultraviolet light under laboratory conditions, installations were devised and set up in schoolrooms, hospital wards, and barracks.

The practical application of ultraviolet light proved on the whole a disappointment.[49-51] The bactericidal action of ultraviolet rays decreases rapidly when the humidity rises above 55 to 60 per cent; the rays are effective only against *small* infectious particles, so that vigorous dust control is also required. Irradiation in effective amounts may cause damage to the skin and conjunctiva. For these reasons and others, constant close supervision by engineering experts was found essential. The results of numerous studies led to the conclusion that ultraviolet light installations may be particularly effective in operating rooms; and that they reduce the velocity of spread of communicable diseases in schools and barracks, but probably not the total incidence. When used in addition to strict aseptic techniques for the control of contact infection, there is little doubt that they further reduce

the incidence of cross-infection in infants' wards.

More or less concurrently with the studies on aerial disinfection by irradiation, other investigations were proceeding, particularly in England, on the properties of germicidal mists and vapors. After Lister's brief use of carbolic air sprays in operating rooms, the use of chemicals for air sterilization was not resumed until 1928.[52] During the ensuing years halogens, hypochlorites, lactic acid, and hexylresorcinol were employed.[53] While in many instances effectively bactericidal, most of these substances were so irritating as to preclude their widespread use. Robertson's[54] discovery of the bactericidal properties of the glycols, previously employed simply as solvents for hexylresorcinol, gave a tremendous impetus to the study of germicidal mists. These chemicals (particularly triethylene glycol) appeared, upon preliminary trial in the laboratory, admirably suited for large-scale air-sterilization. Tasteless, nontoxic, and nonirritating, they are rapidly effective against a wide variety of pathogenic bacteria and viruses. They were soon subjected to practical tests in various types of environment: hospital wards, barracks, and business offices. As in the case of ultraviolet irradiation, certain limitations soon became apparent under these conditions, which had not been foreseen on the basis of laboratory trials. Again it was found necessary to control the humidity of the environment within a rather narrow range; it was important to maintain continuously an adequate glycol concentration, a condition difficult to fulfill since there is no commercially available apparatus for accurate glycol determinations. Moreover, glycol vapor, like ultraviolet rays, cannot sterilize large particles, hence the need for dust control. And finally, expert engineering supervision is required to install the vaporizing equipment and maintain its efficiency. Glycol vapors do display two distinct advantages over ultraviolet rays: they are not injurious to man, and they do diffuse readily throughout the atmosphere of an enclosed space, whereas ultraviolet rays do not. Nevertheless glycol vapors have in actual use been disappointing: while they may reduce the bacterial contamination of the air, there is as yet no conclusive evidence that the actual occurrence of clinical infections is reduced.[51, 55, 56]

During the course of the studies on aerial disinfection with ultraviolet irradiation and glycol vapors, it repeatedly became evident that dust is an important source of infectious particles, and that these larger particles are relatively impervious to germicidal rays and vapors. It is probably in part this realization which led to intensive and productive studies, on both sides of the Atlantic, concerning the fate of infectious particles expelled from the respiratory tract, skin, etc., the rate at which they fall to the floor, persist and recirculate. It had been known for years that large numbers of pathogenic bacteria could be found in the dust of homes and hospital wards.[57] Attention had been focussed particularly on the tubercle bacillus,[58] diphtheria bacillus,[59] hemolytic streptococcus,[60] pneumococcus.[34, 60] More recently it has been shown that at least two viruses, influenza A[61] and variola,[62] can survive up to ten days in dust. In fact, large numbers of the microorganisms expelled from the respiratory tract in droplets fall to the

floor within a radius of nine feet and are incorporated into dust. Thence they may at some future time be raised into the air again by activities such as sweeping, bedmaking, and dressing,[53, 63, 64] only to settle out again on the furniture, toys, floor, as well as on the hands, clothes, and skin of patients and attendants. Such continuing cycles are well established in the case of hemolytic streptococci and Aerobacter bacilli,[6] and these undoubtedly are merely specific examples of a general phenomenon. That the degree of contamination of the air is directly correlated with the degree of activity within an enclosed space has been shown repeatedly.

Since dust must obviously be of major importance in the spread of infection, extensive studies on dust control measures have been carried out both in England and in the United States. The most effective means of dust control seems to be the application of oil to floors, and of oil-in-water emulsions to bedclothes and other fabrics. These procedures, when carefully carried out, result in a marked decrease in "dustiness," without unpleasant side-effects so far as patients and hospital personnel are concerned.[65] Unfortunately the evidence as to the effectiveness of this type of dust control in prevention of cross-infection is limited to one hospital study where the incidence of streptococcal cross-infections in an "oiled" ward appeared to be much lower than that in the control ward.[31]

In the course of the intensive thought devoted during the war and postwar years to possible mechanisms of cross-infection, there arose the very important concept of the "*dangerous carrier*" of pathogenic organisms. The studies of Hare,[66] and of Hare and Mackenzie,[67] also of Hamburger and associates[63] showed that many individuals who are carriers of pathogenic organisms such as hemolytic streptococci do not, in fact, expel very large numbers of these organisms or disperse them widely. They found that, on the whole, talking and even coughing dispersed very few organisms, while sneezing dispersed a great many.[68, 69] Hare,[66] as well as Hamburger, Green, and Hamburger[68] showed that the bedding and clothing of such nasal carriers might be heavily polluted. In one study the bedding of nasal carriers contained eighty times more streptococci than that of throat carriers. The term "dangerous carriers" was given by Hamburger to these individuals who, by virtue of the vast number of infective units which they disperse, heavily contaminate the environment. The concept of the "dangerous carrier" was further elaborated by others[27, 28, 30, 35, 36] who showed that infants with severely infected eczema or with purulent ear discharge or with purulent nasal discharge were readily able to infect their environment and give rise to many secondary cases of infection with the same organism: streptococcus, pneumococcus, Aerobacter, diphtheria bacillus.

Incidental to these studies was the observation that only patients ill with actual infection dispersed microorganisms, therefore the chain of infection appeared to be patient-to-patient, or patient-to-staff, but not staff-to-patient, so long as the staff members were themselves healthy, i.e., not "dangerous carriers."

In addition to the measures used to control contact infection (i.e., "medical asepsis"), air-borne infection, and

dust-borne infection, other attempts at controlling cross-infection have included the administration of gamma globulin or of chemotherapeutic and antibiotic agents to hospital patients exposed to the risk of infection. There is no question that gamma globulin is completely effective for the prophylaxis of measles,[70] and probably helpful in infectious hepatitis,[37, 71] but there is a great deal of doubt as to whether it is of benefit in preventing German measles or chicken pox. Concerning bacterial and viral infections other than those mentioned, there is no satisfactory evidence that gamma globulin is in any way effective.

The evidence concerning the effectiveness of prophylactic chemotherapeutic agents administered to whole groups of individuals is more difficult to evaluate. In many instances the drugs were administered for only a part of the patient's stay in hospital so that he was exposed unprotected the rest of the time.[2] In other studies there is evidence that chemotherapeutic and antibiotic drugs may have been helpful.[55, 72] In the main, there is increasing evidence that these drugs simply complicate the problem by promoting cross-infection due to resistant organisms.[3, 13, 72, 73]

Patients with measles and chicken pox have always presented a special problem in hospitals devoted to the care of children because they seem to be far more infectious than any of the other common diseases, whether bacterial or viral in origin. The reason for this peculiarity is not known, and probably will not be, until satisfactory methods are available for laboratory study of the etiological agents. Perhaps, as in the case of certain viral diseases of animals like hog cholera, the agent is excreted by the patient into his environment in relatively far larger amounts than is the case with, for instance, poliomyelitis, thus rendering these patients "dangerous carriers."

After surveying the available data on cross-infection, including several excellent reviews,[75-79] one is struck with the inadequacy of our information concerning both transmission and prevention. The ideas set forth in the recent memorandum of the Medical Research Council on the "Control of Cross-Infection in Hospitals" differ little from those expressed by Chapin thirty-five years earlier. It seems clear that the prevention of contact infection by "medical asepsis" stands on solid ground. It is also clear that gamma globulin for the prevention of measles is, when properly used, well worth while. As to control of air-borne and dust-borne infections, the most carefully conducted studies have failed to produce convincing evidence that ultraviolet irradiation, oiling of floors, bed linens, and vaporization of glycols can be relied upon to effect a reduction in the number of cross-infections.

Administration of chemotherapeutic and antibiotic drugs to patients for the prevention of bacterial nosocomial infection is a double-edged sword: while it may be effective temporarily under certain conditions, it is likely to give rise to outbreaks of disease due to insusceptible microorganisms and probably is rarely indicated.

The one constructive concept added to our knowledge in recent years seems to be that of the "dangerous carrier": since the patients with heavily infected skins or nasal discharges seem the most dangerous so far as fellow patients and staff are concerned, it would seem logi-

eal to direct particular effort toward isolating this type of patient as strictly as possible. Special attention should probably also be paid to shielding the unusually susceptible individual—premature infant, patient with extensive burns or weeping eczema.

It is hoped that this brief review and historical survey of the ever-present problem of nosocomial infections will serve to emphasize the imperfect state of our knowledge, and to stimulate further investigation in this field.

REFERENCES

1. Barber, Mary, Hayhoe, F. G. J., and Whitehead, J. E. M.: Penicillin-Resistant Staphylococcal Infections in a Maternity Hospital, Lancet **2**: 1120, 1949.
2. Bengtsson, E., and Birke, G.: Complications in Penicillin-Treated Acute Throat Infections Caused by B-hemolytic Streptococci and Among Carriers of Hemolytic Streptococci, Acta med. scandinav. **143**: 120, 1952.
3. Clarke, S. K. R., Dalgliesh, P. G., and Gillespie, W. A.: Hospital Cross-Infections With Staphylococci Resistant to Several Antibiotics, Lancet **1**: 1132, 1952.
4. Elwood, J. S.: Nasal Carriers of Pathogenic Staphylococci in Relation to Penicillin Sensitivity, J. Path. & Bact. **63**: 745, 1951.
5. Keefer, C. S.: Alterations in Normal Bacterial Flora of Man and Secondary Infections During Antibiotic Therapy, Am. J. Med. **11**: 665, 1951.
6. Smith, M. H. D., Loosli, C. G., and Ritter, M. H.: Outbreak of Aerobacter Infections on Infants' Wards, Pediatrics **7**: 550, 1951.
7. Allison, V. D., and Hobbs, B. C.: An Inquiry Into the Epidemiology of Pemphigus Neonatorum, Brit. M. J. **2**: 1, 1947.
8. Miller, A. A.: An Outbreak of Pemphigus Neonatorum in the Maternity Department of a General Hospital, With Special Reference to the Source of Infection, J. Obst. & Gynaec. Brit. Emp. **57**: 415, 1950.
9. Isbister, C: A Clinical Study of Infections of the Newborn Occurring in a Maternity Hospital Over a Six-Month Period, Med. J. Australia **2**: 386, 1951.
10. Coventry, K. J., and Isbister, C.: A Bacteriological and Clinical Study of Infection in Newborn Babies in a Maternity Hospital Nursery, Med. J. Australia **2**: 394, 1951.
11. Felsen, J., Lapin, J., Wolarsky, W., Weil, A. F., and Fox, I.: Staphylococcic Infections in Hospital Nurseries and Pediatrics Wards, Am. J. Dis. Child. **81**: 534, 1951.
12. Thompson, B. A., and Schwabacher, H.: The Incidence of Penicillin-Resistant Staphylococci in a Semiclosed Community, J. Clin. Path. **4**: 350, 1951.
13. Batty Shaw, A., and Mackay, H. A. F.: Double Enteric Infection (la Fièvre Typhoide Intriquée). An account of an Epidemic, J. Hyg. **49**: 299, 1951.
14. Bradley, W. H., Evans, L. W., and Taylor, I.: A Hospital Outbreak of Typhoid Fever, J. Hyg. **49**: 324, 1951.
15. Rubbo, S. D.: Cross-Infection in Hospital Due to Salmonella Derby, J. Hyg. **46**: 158, 1948.
16. Williams, S.: The Bacteriological Considerations of Infantile Enteritis in Sydney, Med. J. Australia **2**: 137, 1951.
17. Watt, J., and Carlton, E.: Outbreak of Salmonella typhimurium Infection Among Newborn Premature Infants, Pub. Health Rep. **60**: 734, 1945.
18. Neter, E.: Observations on the Transmission of Salmonellosis in Man, Am. J. Pub. Health **40**: 929, 1950.
19. Watt, J., and Brown, O. W.: To be published.
20. Sharpe, M. E.: Group D Streptococci in the Faeces of Healthy Infants and of Infants With Neonatal Diarrhoea, J. Hyg. **50**: 209, 1952.
21. Rogers, K. B., and Koegler, S. J.: Inter-Hospital Cross-Infection of Epidemic Infantile Gastro-Enteritis Associated With Type Strains of Bacterium Coli, J. Hyg. **49**: 152, 1951.
22. Smith, J.: The Association of Certain types (Alpha and Beta) of B. coli With Infantile Gastro-Enteritis, J. Hyg. **47**: 221, 1949.
23. Giles, C., Sangster, G., and Smith, J.: An Outbreak of Infantile Gastro-Enteritis in Aberdeen. The Association of a Special Type of B. coli With the Infection, J. Hyg. **46**: 1, 1948.
24. Neter, E., Webb, C. R., Shumway, C. N., and Murdock, M. R.: Study on Etiology, Epidemiology and Antibiotic Therapy of Infantile Diarrhea, With Particular Reference to Certain Serotypes of Escherichia coli, Am. J. Pub. Health **41**: 1490, 1951.
25. Laurell, G.: Air-borne Infections. VII. Coliform Organisms in the Upper Respiratory Tract of Children, With Particular Reference to Hospital Infections, Acta path. et microbiol. scandinav. **31**: 92, 1952.

26. Laurell, G.: Air-borne Infections. IX. Coliform Organisms in the Upper Respiratory Tract of Children, With Particular Reference to Their Mode of Spreading in a Children's Hospital, Acta path. et microbiol. scandinav **31**: 112, 1952.
27. Laurell, G., Löfström, G., Magnusson, J. H., and Ouchterlony, O.: Investigations on Air and Dust as Vehicles of Infectious Agents With Special Reference to Nosocomial Infections of Hemolytic Streptococci in Children's Wards in the Winter and Spring of 1946, Acta med. scandinav. Suppl. **196**: 602, 1947.
28. Laurell, G.: Air-borne Infections. IV. The Control of Dust-borne Streptococcal Infections in Children's Wards, Acta paediat, **37**: 237, 1949.
29. Laurell, G.: Air-borne Infections. VI. Continued Investigations Into the Control of Dust-borne Streptococcal Infections in Infants' Wards, Acta paediat. **41**: 124, 1952.
30. Loosli, C. G., Smith, M. H. D., Cline, J., and Nelson, L.: The Transmission of Hemolytic Streptococcal Infections in Infant Wards With Special Reference to "Skin Dispersers," J. Lab. & Clin. Med. **36**: 342, 1950.
31. Wright, J., Cruickshank, R., and Gunn, W.: The Control of Dust-borne Streptococcal Infection in Measles Wards, Brit. M. J. **1**: 611, 1944.
32. Roberg, N. B.: An Epidemic Caused by a Sulfadiazine-Resistant Strain of Streptococcus Hemolyticus (Group A, Type 17), J. Infect. Dis. **78**: 135, 1946.
33. Guthrie, K. J., and Montgomery, G. L.: Seven-year Study of Pneumococcus. Type Incidence in the Royal Hospital for Sick Children, Glasgow, J. Hyg. **46**: 123, 1948.
34. Finland, M.: The Spread of Pneumococcal and Streptococcal Infections in Hospital Wards and in Families, Aerobiology, Publication No. 17, Am. Assoc. for Advancement of Science, p. 212, 1942.
35. Loosli, C. G., Smith, M. H. D., Ritter, G., and Nelson, L.: Transmission of Pneumococcal Infections on Infants' Wards, to be published.
36. Ouchterlony, O.: Air-borne Infections. III. Infection and Spreading of Infection in Diphtheria With Special Reference to Isolation Wards, Acta med. scandinav. **134**: 296, 1949.
37. Capps, R. B., Bennett, A. M., and Stokes, J., Jr.: Endemic Infectious Hepatitis in an Infants' Orphanage. I. Epidemiologic Studies in Student Nurses, Arch. Int. Med. **89**: 6, 1952.
38. Bennett, A. M., Capps, R. B., Drake, M. E., Ettinger, R. H., Mills, E. H., and Stokes, J., Jr.: Endemic Infectious Hepatitis in an Infants' Orphanage. II. Epidemiologic Studies in Infants and Small Children, Arch Int. Med. **90**: 37, 1952.
39. Capps, R. B., and Stokes, J., Jr.: Epidemiology of Infectious Hepatitis and Problems of Prevention and Control, J. A. M. A. **149**: 557, 1952.
40. Papers of Charles V. Chapin, M. D., published by the Commonwealth Fund, New York, 1934.
41. McNeill, R.: The Prevention of Epidemics and the Construction and Management of Isolation Hospitals, Philadelphia, 1895, P. Blakiston's Son and Company.
42. Semmelweis, I. P.: Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebers, Pest, 1861.
43. Grancher, J. J.: Antisepsie Médicale, Paris, 1888.
44. Hutinel, V.: La diphtérie aux Enfants-Assistés de Paris; sa suppression; étude de Prophylaxie Rev. mens. d. mal. de l'enf. **12**: 515, 1894.
45. Fluegge, C.: Ueber Luftinfection, Ztschr. f. Hyg. u. Infectionskrankh. **25**: 179, 1897.
46. Wells, W. F., and Stone, W. R.: On Air-borne Infection. Study III. Viability of Droplet Nuclei Infection Am. J. Hyg. **20**: 619, 1934.
47. Wells, W. F., and Wells, M. W.: Air-borne Infection as a Basis for a Theory of Contagion, Aerobiology, Publication No. 17, Am. Assoc. for the Advancement of Science, p. 99, 1942.
48. Wells, W. F., and Fair, G. M.: Viability of B. coli Exposed to Ultra-violet Radiation of Air, Science **82**: 280, 1935.
49. Bourdillon, R. B., and Lidwell, O. M.: Field Trials With Ultra-violet Radiation, in Studies in Air Hygiene, Special Report Series No. 262, Medical Research Council, 1948.
50. The Present Status of the Control of Air-borne Infections, Report of the Subcommittee, Am. J. Pub. Health **37**: 13, 1947.
51. Progress in the Control of Air-borne Infections. Report of the Subcommittee, Am. J. Pub. Health **40**: Part II: 82, 1947.
52. Douglas, S. R., Hill, L., and Smith, W.: Effect of Antiseptic Sprays on the Bacterial Content of Air, J. Indust. Hyg. **10**: 219, 1928.
53. Bourdillon, R. B., Lidwell, O. M., Lovelock, J. E., and others: Several papers in Studies in Air Hygiene, Special Report Series No. 262, Medical Research Council, 1948.
54. Robertson, O. H., Bigg, E. Miller, B. F., and Baker, F.: Sterilization of Air by Certain Glycols Employed as Aerosols, Science **93**: 213, 1941.
55. Loosli, C. G., Smith, M. H. D., Gauld, R. L., Robertson, O. H., and Puck, T. T.: Control of Cross-Infections in Infants' Wards by Use of Triethylene Glycol Vapor, Am. J. Pub. Health **37**: 1385, 1947.

56. Krugman, S., and Ward, R.: Air Sterilization in an Infants' Ward, J. A. M. A. **145**: 775, 1951.
57. Thomas, J. C.: Infection From Dust, Lancet **1**: 433, 1941.
58. Neufeld, F.: The Significance of Cough Droplets and Dry Dust in the Spread of Tuberculosis, Am. Rev. Tuberc. **15**: 609, 1927.
59. Crosbie, W. E., and Wright, H. D.: Diphtheria Bacilli in Floor Dust, Lancet **1**: 656, 1941.
60. White, E.: On the Possible Transmission of Hemolytic Streptococci by Dust, Lancet **1**: 941, 1936.
61. Loosli, C. G.: Unpublished data.
62. Downie, A. W., and Dumbell, K. R.: Survival of Variola Virus in Dried Exudate and Crusts From Smallpox Patients, Lancet **1**: 550, 1947.
63. Hamburger, M., Jr., Puck, T. T., Hamburger, V. G., and Johnson, M. A.: Studies on the Transmission of Hemolytic Streptococcus Infections. III. Hemolytic Streptococci in the Air, Floor Dust, and Bedclothing of Hospital Wards and Their Relation to Cross-Infection, J. Infect. Dis **75**: 79, 1944.
64. Duguid, J. P., and Wallace, A. T.: Air Infection With Dust Liberated From Clothing, Lancet, **2**: 845, 1948.
65. Loosli, C. G.: Problem of Dust Control for the Disinfection of Air, Am. J. Pub. Health **38**: 409, 1948.
66. Hare, R.: Expulsion of Haemolytic Streptococci by Nasopharyngeal Carriers, Canad. Pub. Health J. **31**: 539, 1940.
67. Hare, R., and Mackenzie, D. M.: The Source and Transmission of Nasopharyngeal Infections Due to Certain Bacteria and Viruses, Brit. M. J. **1**: 865, 1946.
68. Hamburger, M., Jr., Green, M. J., and Hamburger, V. G.: The Problem of the "Dangerous Carrier" of Hemolytic Streptococci. II. Spread of Infection by Individuals With Strongly Positive Nose Cultures Who Expelled Large Numbers of Hemolytic Streptococci, J. Infect. Dis. **77**: 96, 1945.
69. Hamburger, M., Jr., and Green, M. J.: The Problem of the "Dangerous Carrier." IV. Observations Upon the Role of Hands, of Blowing the Nose, of Sneezing, and of Coughing in the Dispersal of these Micro-organisms, J. Infect. Dis. **79**: 33, 1946.
70. Janeway, C. A.: Clinical Use of Products of Human Plasma Fractionation, J. A. M. A. **126**: 674, 1944.
71. Stokes, J., Jr., Farquhar, J. A., Drake, M. E., Capps, R. B., Ward, C. S., and Kitts, A. W.: Infectious Hepatitis: Length of Protection by Immune Serum Globulin During Epidemics, J. A. M. A. **147**: 712, 1951.
72. Snelling, C. E., and Johnson, R.: The Value of Aureomycin in Prevention of Cross-Infection in the Hospital for Sick Children, Canad. M. A. J. **66**: 6, 1952.
73. Rountree, P. M.: Cross-Infection of Surgical Wounds, Med. J. Australia **2**: 766, 1951.
74. Summers, G. A. C.: Penicillin-Resistant Staphylococci; Distribution Among Outpatients, Lancet **1**: 135, 1952.
75. McKhann, C. F., Steeger, A., and Long, A. P.: Hospital Infections. I. A Survey of the Problem, Am. J. Dis. Child. **55**: 579, 1938.
76. Wright, J.: Nosocomial Infections in Children's Wards, J. Hyg. **40**: 647, 1940.
77. Medical Research Council: War Memorandum No. 11, The Control of Cross-Infection in Hospitals, 1944.
78. Cruickshank, R.: Hospital Infection: A Historical Review, Brit. Med. Bull. **2**: 272, 1944.
79. Miles, A. A.: Observations on the Control of Hospital Infection, Brit. Med. Bull. **2**: 276, 1944.

CONGENITAL MALFORMATIONS OF THE HEART

The Clinician's Responsibility in the Selection of Patients for Operation

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THE advent of cardiac surgery brings new responsibilities to the clinician, not only because of the necessity for accurate diagnosis as to the nature of the malformation, but also in the selection of patients for surgery and in the prevention of needless operations.

If the patient is but slightly incapacitated or entirely asymptomatic, in order to justify operation the risk must be minimal and the degree of benefit great. On the other hand, if the patient is severely incapacitated and the prognosis without operation is bad, considerably greater operative risk, for even moderate benefit, is justified.

Careful evaluation and sound advice to the patient are especially important, because in the last ten years there has been a complete change in the philosophy of patients and parents. Formerly there was grave hesitation concerning operations and there was widespread fear of "experimenting" on a patient. Today patients frequently demand operation. They hear of the extraordinary successes. The dark sorrow of the background which makes the success stand out brilliantly is frequently entirely overlooked or but poorly understood. Therefore the physician has a great responsibility in the proper evaluation of his patient. To do so wisely, the physician must not only be able to diagnose the nature of the malformation, but also know the risks, the dangers, and the amount of benefit to be derived from operation and balance these against the prognosis without operation. This is not always easy because the prognosis varies with the nature of the malformation and with the severity of the abnormality. For this reason it is a grave mistake to tell a patient or a parent that the child must have an operation or he will die. If operation is not indicated, it is difficult for the consultant to persuade the parents of the fact. If operation is not possible, irrevocable harm may have been done.

The prognosis, without operation, is usually better than the doctor anticipates. Although some infants die from cardiac failure and some die from anoxemia, many infants survive innumerable attacks of paroxysmal dyspnea. Most infants survive respiratory infections and pneumonia. Children with malformed hearts usually survive the common contagious diseases of childhood as well as do other children.

Operation is only justified in infancy if life is precarious without operation. In general, as long as the infant is growing and gaining normally there is little or no cause for concern. Failure to gain is often the first manifestation of difficulty.

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Cyanosis due to a malformation of the heart is usually indicative of a serious, but not necessarily of a fatal, malformation.

Broadly speaking, the main causes of death in patients with congenital malformations of the heart are cardiac failure, anoxemia, and occasionally cerebral thrombosis secondary to severe polycythemia. Formerly subacute bacterial endocarditis took a heavy toll. This disease can frequently be prevented by the administration of antibiotics or penicillin prior to and immediately following dental extraction or tonsillectomy; furthermore, if the disease does occur, it is now curable. Pulmonary hypertension and abnormalities of the lungs may cause severe or even fatal cardiac strain, but discussion of these conditions is beyond the scope of this paper.

Cardiac failure is almost invariably preceded by cardiac enlargement. For this reason in the noncyanotic group, where anoxemia and thrombosis play no part, the size of the heart and the rate of cardiac enlargement are the two most important factors. Moreover it is important to remember that months are to an infant's life as years are to a child of 10; therefore in infancy it requires close observation to determine the rate of enlargement or at least to be certain that the heart is not rapidly increasing in size.

Fortunately in many instances, although immediately after birth the heart undergoes rapid enlargement due to the load placed on it by the extrauterine circulation, once the heart has adjusted to the altered circulation the load placed on it is a constant one, and enlargement comes to an end. The heart of an infant is larger in proportion to the chest than is that of a child or an adult; consequently growth is in the infant's favor. Even though the heart may be enormously enlarged in infancy, the baby is not necessarily doomed to die at an early age.

If the heart does adjust to its load, slight cardiac enlargement in children need cause no great concern. By the time a person has reached adult life, if he is free from symptoms and without any restriction of activity, with a heart of normal size or even slight cardiac enlargement, he has only a slightly greater chance of death from heart disease than does an individual with a normal heart. He is more subject to subacute bacterial endocarditis, but that danger is seldom completely eradicated by operation and, as previously stated, the disease is now curable.

Patients who show persistent cyanosis may die from anoxemia without cardiac failure and even with no cardiac enlargement. Therefore in such a patient the oxygen saturation of the arterial blood is quite as important as is the heart size. In a number of malformations, such as a tetralogy of Fallot, tricuspid atresia, and a single ventricle with pulmonary atresia, the malformation does not cause cardiac enlargement. Under such circumstances if death occurs, it is almost invariably due to anoxemia. Moreover, frequently an infant who has barely enough oxygen to sustain life, fails to eat and develops a severe anemia. Such an infant may show little or no cyanosis and yet suffer from a severe degree of oxygen unsaturation of the arterial blood. For this reason the

important consideration is not the intensity of the cyanosis, but the severity of the anoxemia.

The oxygen saturation of the arterial blood is of great prognostic importance provided it is properly evaluated. An oxygen saturation of the arterial blood of 30 per cent obtained under basal conditions is far more serious than if it is obtained when the infant is crying. Unfortunately there is an almost universal tendency to regard an extremely low arterial oxygen saturation as a technical error or to consider that the sample must be that of venous blood, and consequently not significant. The findings of an oxygen saturation of 10 per cent or less in any blood sample taken from an extremity should always be regarded as a danger signal. If it is a sample erroneously taken from a femoral or brachial vein, it is seriously low; if it is from arterial blood it is ominously low. The failure to realize how low the arterial oxygen saturation can be and failure to appreciate the danger of anoxemia is the reason why some infants with malformations of the heart die unexpectedly. In my experience, most infants during an attack of loss of consciousness have an arterial oxygen saturation of less than 10 per cent. The corollary of this is also true, namely, if the infant suffers from attacks of paroxysmal dyspnea which progress to loss of consciousness, the arterial oxygen saturation is usually extremely low; the condition is always serious.

When it is impossible to determine the arterial oxygen saturation, the best clinical guide to the infant's condition is weight gain, and whether or not he suffers from episodes of loss of consciousness. So long as the infant gains in weight at the normal rate there is usually no cause for concern. As previously mentioned, with loss of appetite and failure to gain, the infant frequently develops an anemia and this in turn decreases the amount of available oxygen. Therefore in the presence of persistent cyanosis or definite oxygen unsaturation of the arterial blood, every effort should be made to maintain the hemoglobin at a level of 15 grams per 100 c.c. of circulating blood. When the hemoglobin falls to 10 grams per 100 c.c. or lower, repeated small transfusions are usually indicated and may be life saving.

An x-ray of the chest also offers important information. In the presence of persistent cyanosis, with marked reduction in the pulmonary blood flow, the lungs are excessively clear. Polycythemia and the development of collateral circulation go hand in hand. Hence in the absence of polycythemia increased hilar markings are never due to collateral circulation. If the hilar markings are increased and the red blood cell count is normal, the patient does not suffer from decreased pulmonary blood flow. Under such circumstances any operation to increase the circulation to the lungs is contraindicated.

Not infrequently an infant with a tetralogy of Fallot will show no cyanosis and have a normal weight gain for the first few months. Then between 3 to 6 months of age the infant suffers from attacks of cyanosis or paroxysmal dyspnea. If in spite of the attacks of cyanosis the infant

continues to gain weight, the outlook is usually good. If he ceases to gain weight, the condition is much more serious; early operation may be necessary.

Loud murmurs are not usually of serious prognostic importance. Indeed, in the cyanotic infant a harsh systolic murmur commonly carries a good prognosis, whereas the absence of a murmur carries a guarded prognosis. It is the cyanotic infant with a small heart, no murmur, and excessively clear lung fields who is in grave danger of dying from anoxemia. If he develops attacks of paroxysmal dyspnea which progress to loss of consciousness, early operation is almost always indicated. Indeed, the condition is virtually a surgical emergency.

So long as an attack of paroxysmal dyspnea is readily relieved by placing the infant in the knee-chest position, there is little danger of death from anoxemia. If the infant does not respond to this treatment, the inhalation of oxygen may help. If oxygen does not give prompt relief, or if it is not available, morphine (1 mg. per 10 pounds of body weight) should be given. Most infants in whom the attacks of paroxysmal dyspnea and loss of consciousness are due to pulmonary stenosis respond to this treatment. If the infant requires daily administration of morphine, operation is indicated.

In children with a tetralogy of Fallot, the degree of incapacity and the degree of polycythemia are the two most important factors in the consideration of operation. If the patient shows only minimal cyanosis but can walk only a short distance without squatting, the probability is that he suffers from a sharp reduction in the oxygen saturation of the arterial blood upon exercise. If such is the case, he can usually be greatly helped by operation.

An extreme polycythemia, although it develops to compensate for anoxemia, increases the danger of thrombosis. Thromboses may occur anywhere; many are fatal and others cause severe incapacity, hemiplegia, or blindness. Therefore every precaution possible should be taken to prevent thrombosis. The danger may be eliminated by successful surgery. Furthermore the results of operation are better for a child or youth than for an adult with long-standing polycythemia. Moreover, the long-time results are far better for a patient who has obtained a good result from operation than for one who has only obtained a fair result. For this reason marked or increasing polycythemia is an indication for operation.

When operation is not possible, every effort should be made to maintain adequate fluid intake and to prevent dehydration, because this lessens the danger of hemoconcentration and thereby lessens the danger of thrombosis. Because of this danger a child or adult with a red blood cell count of over 7 million should receive 2,500 to 4,000 c.c. of fluid every twenty-four hours and never be without fluid for more than twelve hours. This simple precaution does much to prevent cerebral thrombosis. Indeed, I do not think it is chance that the only two cyanotic patients whom I have known to become blind were French children. French children, by and large, receive a low fluid intake as they do not drink water and

children are not given much wine, and they are rarely given milk.

Pure pulmonary stenosis is another malformation which can be helped by surgery. Although a mild to moderate degree of pulmonary stenosis may be compatible with a long and active life, severe pulmonary stenosis may lead to cardiac failure and death within the first year.

Infants with severe pulmonary stenosis generally show cyanosis at birth due to the physiological patency of the foramen ovale. The persistence or disappearance of cyanosis depends upon the extent to which the valve covering the foramen ovale becomes sealed. Patency of the foramen ovale acts as an escape valve for the high pressure in the right ventricle. Therefore there is greater danger of cardiac enlargement if the cyanosis is markedly reduced or disappears than if it persists. It is important to remember that this malformation may lead to progressive cardiac enlargement. Hence, an infant suspected of this malformation should be kept under close observation for the first two years of life. Since cardiac enlargement precedes symptoms, even though the infant may appear healthy and gain weight normally, his heart may be undergoing progressive enlargement. Serial x-rays at monthly intervals are of great help in the evaluation of the infant's condition.

If the heart becomes greatly enlarged or if the infant develops pulsations at the margin of the liver, early operation is indicated. If the heart remains normal in size and the infant's color is good, it is wise to postpone operation. Such a patient should be observed at regular intervals and special care be taken during the spurt of growth which occurs at puberty and during adolescence. In children and young adults, evidence of increase in heart size is an indication for operation.

There are, however, all grades of pulmonary stenosis. Not infrequently the condition is so mild that there is no evidence of cardiac enlargement or cardiac strain and the diagnosis is established by catheterization. If the pressure in the right ventricle is under 100 mm. of mercury and the patient has a heart of normal size and is asymptomatic on full activity, operation is not indicated. Indeed, under such circumstances cutting the pulmonary valve may lead to pulmonary insufficiency or even to subsequent scarring of the pulmonary valves and eventually to an increase in the pulmonary stenosis; therefore, in my opinion operation for these patients is contraindicated.

In the group of malformations which do not cause cyanosis, there are three; namely, a patent ductus arteriosus, coaretation of the aorta, and a vascular ring, which are now amenable to surgery. In each of these, operation may be of great benefit.

An uncomplicated patent ductus arteriosus is virtually the only malformation in which operation is usually indicated. Even in this malformation if the heart is completely normal in size and there is no evidence of cardiac strain, I doubt that ligation or division of the ductus arteriosus is indicated in an infant under 2 years of age, or in an adult over 45 years. In the former in-

stance the ductus arteriosus may yet close spontaneously; in the latter the danger of subacute bacterial endocarditis is virtually the only reason for operation. Although the danger of such an infection is markedly reduced by operation, we have not yet proved that with ligation or division of the ductus arteriosus both the aorta and the pulmonary artery heal so smoothly that the danger of subacute bacterial endocarditis is entirely eliminated. Indeed, even after successful ligation of the ductus arteriosus, I still advise a patient to receive prophylactic penicillin or other antibiotics prior to dental extraction or tonsillectomy. When we have a means of prevention, why take the slightest chance!

Coarctation of the aorta is another malformation in which operation may restore the circulation to normal. Operation is only indicated in infancy if the infant develops cardiac failure which does not respond to digitalis and other medical treatment. In older patients severe hypertension, left ventricular strain, or aortic insufficiency are definite indications for operation. Although operation is easier and the chance of success is better in childhood than in adult life, if the blood pressure is normal and there is no evidence of left ventricular strain, and the condition is picked up on routine examination, the risk of operation must be balanced against the possible future benefit.

A vascular ring which causes symptoms in early infancy is virtually a surgical emergency, whereas if the condition is asymptomatic and is picked up on x-ray or fluoroscopy, there is no need for operation and no benefit to be derived therefrom. The condition is compatible with a long and active life.

It is important to remember that a cardiac operation is of benefit only to the heart and circulation. Lack of oxygen to the brain does not cause mental retardation. The converse of this is also true—improvement in the oxygen supply to the brain does not improve mentality. Furthermore, the physically strong, mentally weak child can get into far more trouble in this world than the mentally deficient child who is also physically handicapped.

The proper handling of the infant or child is important. If the mother is given a hopeless prognosis, she naturally and inevitably spoils the child and even though he may be rehabilitated at a later age, the psychological damage done is well nigh impossible to overcome. My social worker, Mrs. Mildred White Solomon, made a study of "how blue babies adjust to operation." She found the adjustment after operation varied with the adjustment before operation. My own experience is entirely in agreement with this observation; the well-adjusted, wisely handled, severely handicapped child blossoms after operation, whereas the spoiled child will seek other ways of demanding attention. Therefore, the more normal the child's life can be, the better it is for the child and the parent.

Whenever possible the child should attend a regular school. He should be encouraged to play and develop his physical strength. It is in cases of severe pulmonary stenosis or aortic stenosis that exercise may place a strain on the heart. In a

patient with pulmonary stenosis, evidence of progressive cardiac enlargement is an indication for operation. In patients with aortic stenosis, since operation is not yet possible, restriction of activity may be necessary. With other malformations the patient usually limits his own activity; it is seldom necessary for the doctor or parent to do so.

Furthermore, we should all remember that "we know not what is to come." Even though a malformation is not operable today, it may be amenable to surgery within the lifetime of that individual. For this reason the existence of a cardiac malformation is seldom, if ever, justification for sterilization. Sad is the situation when a young woman is referred to the doctor with an operable malformation and the doctors say, "We are glad to be able to restore the heart to normal," and she replies, "What is the use—I can no longer have a child."

Finally, a word concerning the new operations which are constantly appearing on the horizon. If the patient is asymptomatic and the heart is not greatly enlarged, there is no need to urge a new operation. Such a patient is in no immediate danger. Furthermore, experience has shown that with any new operation the risk of surgery decreases sharply during the first few years. Therefore it is only the seriously incapacitated patient who should be submitted to a new operation. Let us point out the hope of the future. When hope is near, wait its safe development; when hope is distant, make the mother realize that in spite of a physical handicap many individuals can lead happy, significant lives and take their place as respected, useful citizens in the world.

THE DIAGNOSIS OF THE ADRENOGENITAL SYNDROME AND ITS TREATMENT WITH CORTISONE

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THE adrenogenital syndrome may be due to either an adrenocortical tumor or adrenal hyperplasia. The administration of cortisone has proved of value not only in the treatment of adrenal hyperplasia but also as a diagnostic aid in differentiating adrenal hyperplasia from tumor.

TYPES OF THE DISORDER

The clinical manifestations of the adrenogenital syndrome vary with the sex of the patient and the time the disorder begins.[1] The congenital form is due to hyperplasia, the postnatal form to either tumor or hyperplasia. In congenital adrenal hyperplasia, there are a number of variations in the hormonal manifestations. In all cases there are virilization and increased protein anabolism due to excessive secretion of androgen. There are, however, differences in respect to the other functions of the adrenal cortex. Although most patients show no evidence of disturbed sodium and potassium regulation, some have a tendency to Na loss and elevation of serum K which may lead in early life to death from dehydration and circulatory collapse or from cardiac arrest.[2, 3] Occasionally patients with the adrenogenital syndrome have hypertension without demonstrable abnormality of the electrolytes.[4, 5] Finally several patients without electrolyte disturbance have shown a tendency to hypoglycemia.[5, 6] To some extent the adrenal pathology can be correlated with these differences in symptoms. The enlargement of the adrenals is caused principally by hyperplasia of the reticular zone which is believed to be responsible for the secretion of androgen. The fasicular zone is more or less disorganized and infiltrated with reticular zone cells. The zona glomerulosa may be absent, particularly in patients who have a tendency to sodium loss,[2, 3] but has been reported to be hypertrophied in two patients who had hypertension in addition to precocious virilization.[4, 5]

DIAGNOSIS

Females With Congenital Adrenal Hyperplasia.—When the disorder begins in embryonic life there are abnormalities of sex differentiation which can be recognized at birth. There is a hypertrophied phallus which resembles a hypospadic penis and usually there is a persistent urogenital sinus which communicates anteriorly with the urethra and posteriorly with the vagina, uterus, and tubes.[1] Occasionally,

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however, there are separate urethral and vaginal orifices. The appearance of the external genitals varies considerably depending upon the degree of separation or fusion of the labial folds. However, the diagnosis of female pseudohermaphroditism due to congenital adrenal hyperplasia cannot be based on these findings because the same anatomic abnormalities may occur in some genetic intersexes who have either testes, ovotestes, or ovaries. As shown in Table I, the differentiation of congenital adrenal hyperplasia from genetic intersexuality depends upon the fact that in the former the excessive secretion of adrenal androgen causes a high excretion of urinary 17-ketosteroids, accelerated growth and osseous development, and precocious growth of sexual hair. Elevation of the 17-ketosteroids to levels of 2 to 6 mg. per day can be demonstrated as early as the first few months of life. Genetic intersexes, on the other hand, do not show either androgenic or estrogenic manifestations until the age of puberty.

TABLE I. DIFFERENTIAL DIAGNOSIS OF ADRENAL HYPERPLASIA AND TUMOR IN FEMALES

	ABNORMALITY OF EMBRYONIC SEX DIFFERENTIATION	EVIDENCE OF EXCESSIVE ANDROGEN			RESPONSE OF 17-KS TO CORTISONE
		INCREASED 17-KS	EXCESSIVE GROWTH AND OSSEOUS DEVELOPMENT	PRECOCIOUS SEXUAL HAIR	
Congenital adrenal hyperplasia (Female pseudohermaphroditism)	Hypertrophied clitoris Persistent urogenital sinus (usually)	+	+	+	+
Genetic intersexes with testes, ovotestes, or ovaries	Various abnormalities (including the above)	0	0	0	0
Postnatal					
Adrenal tumor	Normal at birth Later virilization and hirsutism	+	+	+	0
Adrenal hyperplasia	Same	+	+	+	+
Constitutional hirsutism or "premature pubarche"	None	0 or ±	0	±	0

Females Developing the Adrenogenital Syndrome Postnatally.—The onset of virilization postnatally in a prepuberal girl who has previously been entirely normal is strongly suggestive of adrenal tumor. We have, however, seen one girl who began to virilize rapidly at the age of 5 years and who had bilateral adrenal hyperplasia. The early appearance of sexual hair without enlargement of the clitoris or other secondary sex development may represent merely a benign variation in the pattern of adolescent development which we have termed "premature pubarche."[7] In postpuberal females the adrenogenital syndrome may be due to either diffuse hyperplasia of the adrenals or to adrenal tumor. It must be differentiated from constitution types of hirsutism by the demonstration of elevated 17-ketosteroids and from arrhenoblastoma of the ovary by pelvic examination.

The differentiation of adrenal tumor and hyperplasia can be made by studying the effect of the administration of cortisone on the 17-ketosteroid excretion. Cortisone causes a marked suppression of the urinary 17-ketosteroids in cases of adrenal hyperplasia but has little or no effect in those due to

adrenal tumor.[8, 9] Likewise a high output of dehydroisoandrosterone or other 3-β-hydroxy-ketosteroids is strongly suggestive of a neoplasm.[10]

Males With Adrenal Hyperplasia or Tumor.—In males congenital adrenal hyperplasia causes no abnormality of embryonic sex differentiation but leads to early development of male secondary sexual development—a condition known as macrogenitosomia praecox. As shown in Table II this must be distinguished from true sexual precocity due to early idiopathic activity of the pituitary gonadotropic mechanism or to an intracranial lesion. In true sexual precocity, both the interstitial cells of Leydig and the tubules develop and active spermatogenesis may occur. The testes may enlarge to adult size. In adrenal hyperplasia the testes usually remain small and completely immature. In some cases, however, they enlarge to a greater or less degree due to increase in the size of the tubules or to infiltration with aberrant adrenal tissue. Leydig cells do not appear and the tubules do not show spermatogenesis.[2, 11] Testicular biopsies aid in diagnosis. In sexual precocity of constitutional or hypothalamic origin, the urinary 17-ketosteroids rise only to adolescent or adult levels; in the adrenogenital syndrome they may be far in excess of the normal for an adult. The fact that in the congenital type of adrenal hyperplasia the precocious sexual development may not be evident until the patient is 2 or 3 years of age makes it difficult to differentiate this condition clinically from virilizing tumor of the adrenal. The response of the 17-ketosteroids to cortisone and the study of dehydroisoandrosterone are, however, of great diagnostic value.

Table II. Differential Diagnosis of Adrenal Hyperplasia and Tumor in Males

	Somatic and sexual development	17-KS	Testes	Response of 17-KS to cortisone
Adrenal hyperplasia	Excessive	Excessive	Immature or infiltrated	+
Adrenal tumor	Excessive	Excessive	Immature	0
Sexual precocity (constitutional or intracranial origin)	Excessive	Adolescent levels	Mature	0
Interstitial cell tumor	Excessive	Excessive	Tumor	0

TREATMENT

Prior to the use of cortisone it was impossible to check the progressive virilization and excessive growth which occur in cases of adrenal hyperplasia. Removal of as much as one and one-half of the adrenal glands has been of no value. The administration of large amounts of estrogen to female pseudohermaphrodites may cause breast development and its withdrawal may lead to uterine bleeding. It does not decrease the hirsutism or check the virilization. We have attempted without success to suppress the secretion of adrenal androgen by the administration of 17-ethyl testosterone, 17-vinyl testosterone, 17-methyl androstenediol and 17-methyl androstanediol, steroids which have a chemical structure similar to androgens but relatively little virilizing activity.

In January, 1950, a female pseudohermaphrodite of 15 years was first treated with intramuscular cortisone in doses of 100 mg. per day.[12] The urinary 17-ketosteroids fell promptly from an average of 42 mg. per day to an average of 6.4 mg. per day. After fifteen days cortisone was discontinued. A period of twelve days then elapsed before the 17-ketosteroids began to rise to the previously high level. The excretion of estrogens determined fluorometrically followed the same pattern as the 17-ketosteroids. The urinary corticosteroids decreased during the first ten days of treatment but then increased, probably due to the fact that some of the administered cortisone was excreted in this fraction. It was shown subsequently that the suppression of

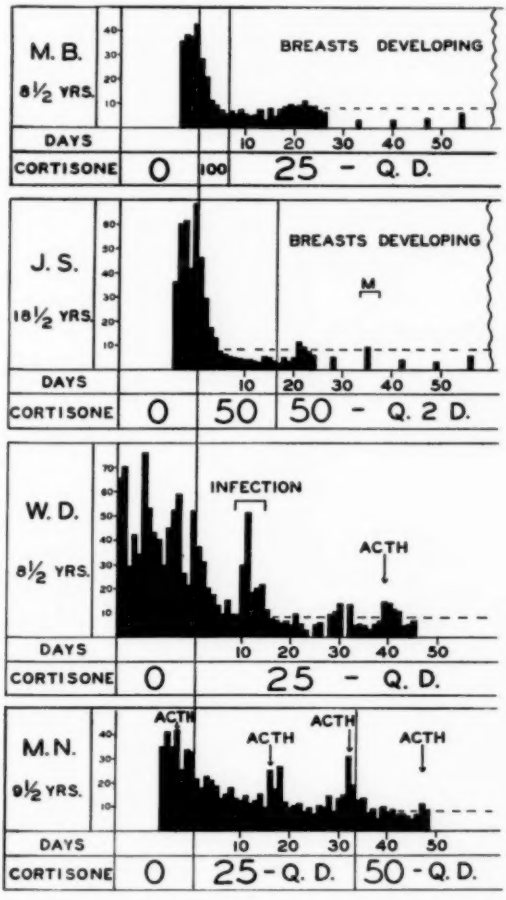

Fig. 1.—Comparison of the effects of initial doses of 100 mg., 50 mg., and 25 mg. of intramuscular cortisone on the suppression of urinary 17-ketosteroids of four female pseudohermaphrodites. (Black bars represent output of 17-ketosteroids in milligrams per day). (From J. Clin. Endocrinol. & Metab. 12: 257, 1952.)

TABLE III. EFFECTS OF CORTISONE ON

NAME AND NO.	SEX	ASSOCIATED SYMPTOMS	BEFORE TREATMENT			
			AGE (YR.)	BONE AGE (YR.)	HIRSUTISM	17-KS (MG./D.)
1. J. St.	F	Hypertension Pigmentation	18½	Fused	+++	53
2. M. St.	F	Hypertension Pigmentation	16¼	Fused	+++	62
3. P. Ro.	F		16	Fused	+++	50
4. M. No.	F		10½	16	++	34
5. W. De.	F		9¼	15	++	38
6. M. Be.	F		8½	17	++	34
7. E. No.	F	Postnatal virilization at 5 yr.	6½	11	++	15
8. T. Tw.	F		6¼	11	+	11.5
9. B. Th.	F		21 mo.	3	±	4.6
10. F. F.	F	Salt loss	4½ mo.	13 wk.	0	4.8
11. S. K.	F	Salt loss	2½ mo.		0	3.2
12. L. U.	F	Salt loss	2½ mo.	9 wk.	0	3.5
13. D. Br.	M		8¾	14	++	27
14. T. Tw.	M		6¾	13½	++	26
15. M. De.	M		6¾	13	++±	40
16. W. De.	M		5¾	11	+++	18
17. A. Br.	M		4	9½	+	8.5
18. W. Je.	M	Hypertension Cardiac failure	3½	11	±	8.6
19. S. Bo.	M	Salt loss	3½	10½	+	48

*100/4=25 indicates that 100 mg. were injected every fourth day, which is equivalent to 25 mg. daily.

25×3=75 indicates that 25 mg. were given three times a day—a total of 75 mg. daily.

†(F) indicates that Compound F was used in treatment instead of cortisone.

the 17-ketosteroids and chemically measured estrogens was paralleled by decrease of biologically active androgens and estrogens in the urine.

The effects of 100 mg. of cortisone daily were so striking in the first experiment that it was decided to try smaller doses in the hope that equal suppression of the abnormal adrenal activity might be brought about by amounts of cortisone which approximated the normal secretion of glycogenetic corticoids. It was soon shown that in female pseudohermaphrodites over 8 years of age initial doses of 50 or 25 mg. of intramuscular cortisone daily were as effective as 100 mg. per day in causing adrenal suppression (Fig. 1). It appeared that 25 mg. of intramuscular cortisone daily would maintain this suppression in the older patients and that considerably smaller amounts were required in infants.

Since in preliminary studies on five patients who were treated for periods up to forty-five days no abnormal metabolic or toxic effects were encountered, in June, 1950, continuous treat-

PATIENTS WITH ADRENAL HYPERPLASIA

MAINTENANCE CORTISONE			DURATION	RESULTS			
I.M. (MG.)	ORAL (MG.)	OTHER TREATMENT	RX (MO.)	17-KS (MG./D.)	BREASTS	MENSTRUATION	OTHER RESULTS
100/4 = 25*			27½	4.9	+	+	Normal B. P. Depigmentation
100/4 = 25			23	5.0	+	↓	Normal B. P. Depigmentation
	25 × 3 = 75*		22½	5.6	+	+	
	25 × 2 = 50		16	4.8	+	+	
	25 × 2 = 50		20	4.0	+	+	
75/3 = 25			28	4.4	+	0	
	(F) 12.5 × 3 = 37.5†		8	1.8	+	0	
50/3 = 16.6			9	1.5	+	0	
(F) 25/3 = 8.3			5	0.7	0	0	
	5 × 4 = 20	NaCl 3 Gm.	21	1.2	0	0	Normal electrolytes Normal growth
37.5/4 = 9.4		NaCl 3 Gm. DCA pellets	20	1.3	0	0	Normal growth & electrolytes
25/3 = 8.3		NaCl 3 Gm. DCA pellets	25½	0.3	0	0	Normal growth & electrolytes
					TEST. DEVELOPMENT		
75/3 = 25			8	6.1	+		
100/5 = 20			17	3.0	+		
(F) 50/2 = 25			12	5.2	+		
	25 × 2 = 50		12	1.9	+		
50/4 = 12.5			8	1.9	0		
	12.5 × 2 = 25		21	0.8	0?		Normal B. P.
	25 × 2 = 50	NaCl 4 Gm.	11	5.1	?		Normal electrolytes

ment with cortisone was begun in a series of patients with the adrenogenital syndrome. The present discussion is based on observations made on nineteen patients who now have been under continuous therapy with cortisone for periods ranging from five to twenty-eight months. Twelve were female pseudohermaphrodites and seven were males with macrogenitosomia praecox. As shown in Table III the ages at the time treatment was begun ranged from 2½ months to 18½ years.

Dosage of Intramuscular and Oral Cortisone.—The plan of treatment has been to suppress the activity of the abnormal adrenals as rapidly and as completely as possible and then to determine in each case the minimum dose which is necessary to maintain this suppression.[13] The level of urinary 17-ketosteroids serves as a guide to the degree of suppression. In patients over 8 years of age it has proved impossible to reduce the ketosteroid output below 4 to 6 mg. per day. In very young infants it may be decreased to 0.5 mg. or less, but in children between 1 and 6 years the minimal values obtained have been from 1 to 3 mg. per day. Perhaps these amounts represent metabolic products of the administered cortisone.

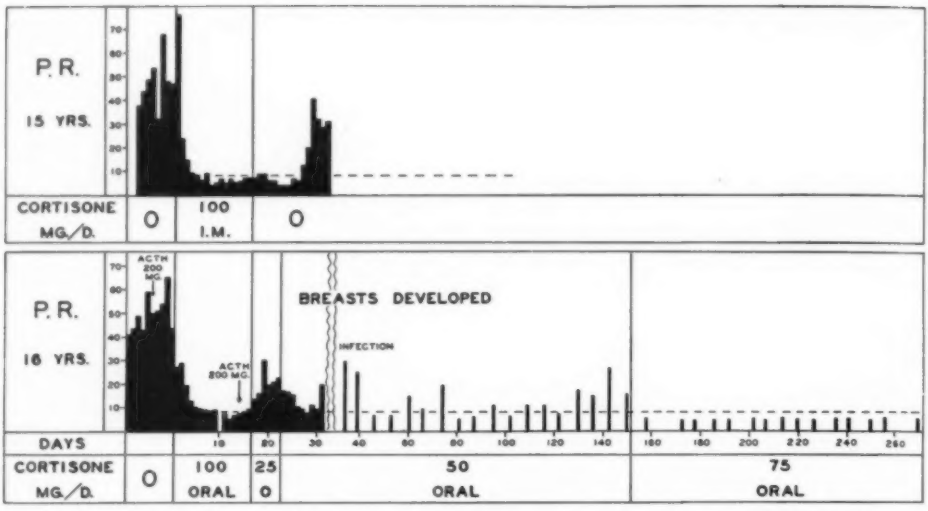

Fig. 2.—Comparison of the effects of intramuscular and oral cortisone on the suppression of urinary 17-ketosteroids of a female pseudohermaphrodite. In doses of 100 mg. daily both oral and intramuscular cortisone caused prompt suppression, but 75 mg. of oral cortisone daily (25 mg. three times a day) were required to maintain the ketosteroid output below 8 mg. per day. (From J. Clin. Endocrinol. & Metab. 12: 257, 1952.)

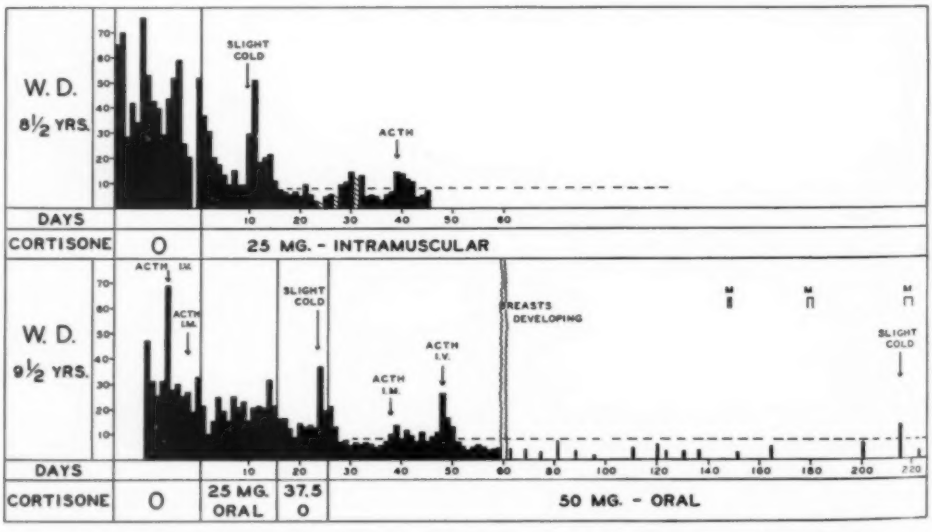

Fig. 3.—Comparison of the effects of intramuscular and oral cortisone on the suppression of urinary 17-ketosteroids of a female pseudohermaphrodite. Note the temporary increases in ketosteroid excretion which occurred during slight colds and the relatively smaller responses to test doses of intramuscular or intravenous ACTH given over periods of twenty-four or twelve hours ("M" represents menstrual periods). (From J. Clin. Endocrinol. & Metab. 12: 257, 1952.)

To obtain the *initial suppression* of adrenal activity we have preferred intramuscular rather than oral cortisone because the results are more predictable. We have given 50 mg. daily to older children and 25 mg. per day to infants under 2 years. Maximum suppression is usually attained within five to ten days, after which the amount of cortisone administered should be reduced to the *maintenance dose* which must be determined in each case. This necessitates frequent and repeated measurements of the urinary 17-ketosteroids.

A comparison of intramuscular and oral administration in the same and in different cases has shown that two or three times as much cortisone is required when it is given orally in two or three divided doses as shown in Figs. 2, 3, 4. The reason for this is that the effects of oral cortisone are transient and probably wear off during the night. On the other hand, intramuscular cortisone is absorbed slowly, so that when a depot is once established its effects may not disappear for ten to twelve days. Accordingly an injection of 100 mg. given every fourth day is as effective as 25 mg. daily.

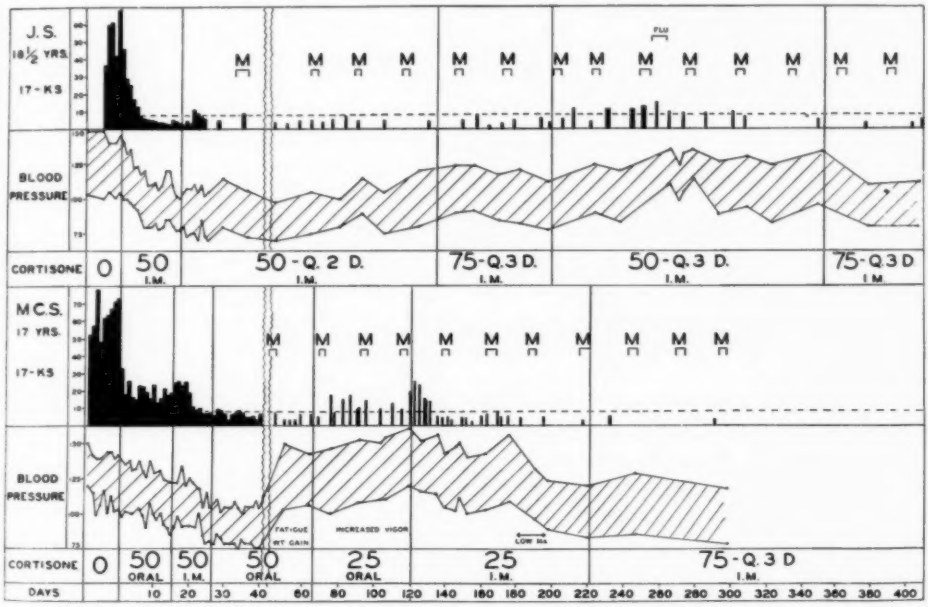

Fig. 4.—Comparison of the effects of oral and intramuscular cortisone on the urinary 17-ketosteroids and the blood pressure in two sisters with female pseudohermaphroditism. ("M" represents menstrual periods.) (From J. Clin. Endocrinol. & Metab. 12: 1015, 1952.)

The maintenance doses of cortisone as shown in Table III vary somewhat according to the age of the patient. The maximum requirement of cortisone injected intramuscularly is 25 mg. per day. This may be given as 75 mg. every third day or 100 mg. every fourth day. The corresponding dose of cortisone given orally is 50 to 75 mg. per day, divided so that the patient re-

ceives 25 mg. two or three times a day. In some of the youngest infants adrenal suppression has been maintained by 25 mg. of cortisone injected intramuscularly every third day (equivalent to 8.3 mg. daily), 37.5 mg. every fourth day (equivalent to 9.4 mg. daily), or 5 mg. of oral cortisone four times a day (20 mg. daily). The requirement for children between 2 and 8 years varies in different cases between these extremes of dosages and must be determined in each case.

RESULTS OF CORTISONE THERAPY

The results of cortisone therapy depend upon the sex of the patient and the age, particularly the "developmental age" as measured by the osseous development, which has been attained before treatment is begun.[14]

Girls.—As shown in Table III, there were six female pseudohermaphrodites between the ages of 8½ and 18½ years (Cases 1 to 6). They all had advanced somatic development with bone ages over 15 years so that growth was virtually completed. They showed advanced masculine hirsutism and complete absence of all female development. Under treatment there was definite decrease of the hirsutism. Hair on the face, trunk, and extremities which had been coarse and dark did not disappear entirely but became much lighter and finer, and grew less rapidly. Acne disappeared. All of the patients developed breasts promptly and the vaginal smears became estrinized. Five of the six patients have menstruated with regular periods. In several cases in which basal temperatures were recorded cyclic fluctuations and menstrual cramps suggestive of ovulation and progesterone secretion occurred, and in one progestational endometrium was demonstrated on curretage. The one patient in this group who has not menstruated is now only 10½ years of age. No increase in height has occurred in these patients. There has been moderate increase of weight in several cases but obesity or other evidence of Cushing's syndrome has not resulted. There has been some increase in the fat deposits over the buttocks and breasts causing feminine contours characteristic of adolescence. In two instances (Cases 5 and 6) this occurred so rapidly that pinkish striae developed in the gluteal regions but disappeared later while cortisone therapy was continued. The features became softer, more rounded, and feminine.

Two girls (Cases 7 and 8) were treated at the age of 6¼ years and 6½ years, respectively. The younger was a typical female pseudohermaphrodite. The older had been entirely normal until the age of 5¾ years and then had virilized rapidly. Adrenal hyperplasia had been demonstrated and a neoplasm excluded by exploratory operation. In each case the bone age was 11 years. Each had an enlarged clitoris and a moderate amount of pubic hair, but no hair elsewhere. The 17-ketosteroid excretion was 11.5 mg. and 15 mg. per day, respectively, considerably less than in the older patients studied. Somewhat smaller doses of cortisone brought about a reduction of the ketosteroids to 1.5 and 1.8 mg. per day. In spite of the young chronological age each of these girls began to show adolescent development of the breasts within a few months after cortisone therapy was instituted. The breasts are still quite small. No apparent change in pubic hair has occurred. The patients have continued

to grow fairly rapidly at approximately the normal adolescent rate.

In the third group are four infant female pseudohermaphrodites (Cases 9, 10, 11, 12). Treatment was begun in two at 2½ months, in one at 4½ months, and in another at 21 months. The three younger patients, all of whom had a tendency to Na loss, each had an enlarged clitoris but no pubic hair. The 21-month-old girl was beginning to develop pubic hair. No sexual changes have been observed under cortisone. The principal problem was to regulate the dose of cortisone so as to prevent excessive growth and osseous development without inhibiting these abnormally. One infant (Case 12) received 25 mg. of intramuscular cortisone daily for a period of six months in order to study the effects on electrolyte metabolism. During this time she developed obesity and other signs of Cushing's syndrome, and growth and osseous development were inhibited (Fig. 5). When the dose of cortisone was reduced to 5 mg. per day, the ketosteroid excretion remained suppressed while normal growth and osseous development were resumed. The other three children in this group who were treated with mini-

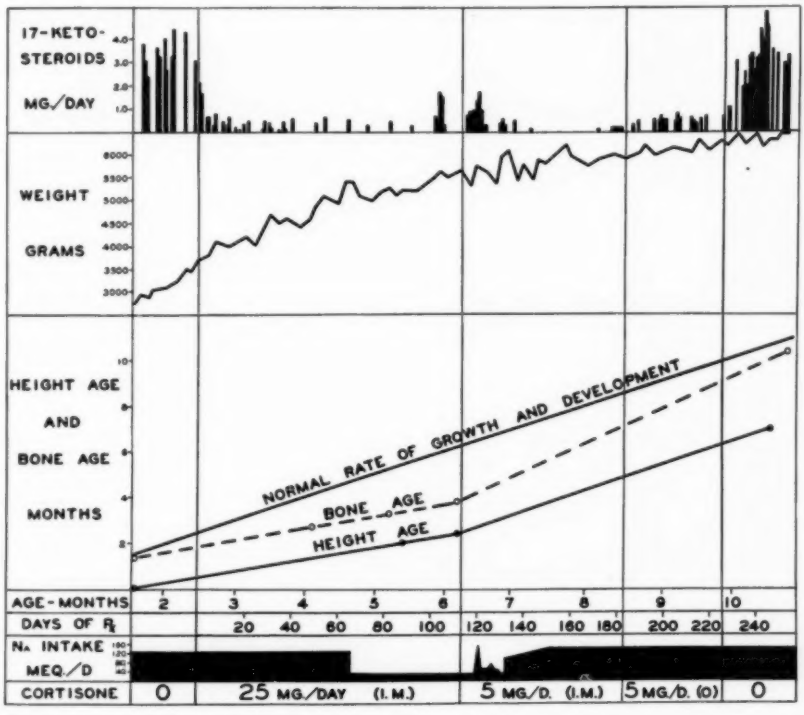

Fig. 5.—Chart shows retardation of rates of growth and osseous development of an infant pseudohermaphrodite while she was receiving 25 mg. of intramuscular cortisone daily and the increase of rates when the dose was decreased to 5 mg. daily which was adequate at this time to maintain suppression of the ketosteroid excretion. (From J. Clin. Endocrinol. & Metab. 12: 277, 1952.)

mum suppressive doses of cortisone have shown normal somatic growth and development.

Boys.—Seven boys with macrogenitosomia praecox have been treated with cortisone. As in the case of girls the effects on sexual development depend upon the level of general somatic development, as measured by the bone age, attained before treatment is begun. The three older boys (Cases 13, 14, 15) who had bone ages between 13 and 14 years, prior to therapy had small immature testes measuring approximately 2.5 × 1.5 cm. After suppression of adrenal activity, the testes promptly underwent development and maturation increasing to 3.5 × 2 cm. or more. The tubules and interstitial cells showed developmental changes which occur characteristically in normal adolescence under stimulation with pituitary LH and FSH. There was no decrease in male sexual characteristics but rather a slow progression, such as occurs in normal adolescence. Growth in stature continued at an adolescent rate. In contrast four younger boys (Cases 16, 17, 18, 19), with chronological ages between 3½ and 5¾ years and bone ages of 9½ to 11 years, showed no enlargement or development of their testes. No changes in secondary sexual development were obvious except that in one (Case 18) there appeared to be some decrease of pubic hair and the size of the penis. Growth and osseous development continued but at a somewhat slower rate than before treatment.

Effects of Cortisone on Hypertension.—Three patients with congenital adrenal hyperplasia, two sisters 16¼ and 18½ years, respectively, and a boy of 3¾ years, had hypertension.[5] In the case of the boy, biopsy of one adrenal showed hyperplasia of the zona glomerulosa similar to that previously described by Shepard and Clausen.[4] The boy had had a greatly enlarged heart with periods of decompensation for two years. No changes in serum electrolytes or blood volume were noted. Suppression of the adrenal hyperactivity with cortisone caused the blood pressure to fall in all cases and it has now remained normal for periods of twenty-one to twenty-seven months. The boy's heart has returned to normal size. In the case of one girl (Case 2) there was a recurrence of the hypertension during cortisone therapy (see Fig. 4). However, the blood pressure again returned to normal on giving a low Na diet for three weeks and subsequently remained normal on a normal diet. In the other cases no salt restriction was necessary.

Effects of Cortisone on Pigmentation of Skin.—The two sisters with hypertension had marked pigmentation of the skin and mucous membranes of an Addisonian type. This faded promptly under cortisone therapy. A number of other patients who had slight degrees of pigmentation showed fading.

Effects of Cortisone on Disordered Electrolyte Metabolism.—Infants with congenital adrenal hyperplasia who have a disorder of electrolyte regulation present the most difficult therapeutic problem. Unless treated properly they die of dehydration or of cardiac arrest due to hyperkalemia. Before the use of cortisone the administration of NaCl together with large doses of desoxycorticosterone controlled the electrolyte disturbance but did not check the progressive virilization characteristic of the disease. The following observations are based on exten-

sive studies on three such cases which have been published elsewhere.[15]

It is striking that whenever the activity of the adrenals, as measured by the output of 17-ketosteroids, is increased during an infection or with the administration of ACTH there is a concomitant loss of Na with a fall of serum Na and rise of serum K. Likewise the infants with congenital adrenal hyperplasia require surprisingly large amounts of DCA and salt to control the electrolyte disorder compared to adults with severe Addison's disease. We believe therefore that the electrolyte defect is not due entirely to a deficiency of the Na-retaining hormone but that the abnormal pattern of adrenal steroids secreted tends to cause an active Na loss.

When cortisone is administered to infants with the combined adrenal disorder in amounts sufficient to suppress the 17-ketosteroid, less DCA and/or NaCl are required to maintain electrolyte equilibrium. This also tends to prevent the salt-losing crises which occur during acute illnesses. Although part of the favorable influence of cortisone may be due to the fact that it has a slight Na-retaining effect similar to DCA, we believe that its major action is to suppress the secretion of the abnormal pattern of adrenal hormones which has a tendency to promote Na loss.

We would make the following suggestions for the treatment of cases of congenital adrenal hyperplasia of the salt-losing type:

1. First, administer large amounts of NaCl (3 to 6 Gm. per day), either parenterally or orally, sufficient to correct the dehydration and other symptoms of sodium deficiency. In the more severe cases this does not correct the serum electrolytes.

2. Next, administer cortisone and adjust the dose to the minimum required to maintain full adrenal suppression. During this time continue with the high NaCl intake.

3. After cortisone therapy has been adjusted, determine the dose of DCA and/or NaCl required to maintain normal serum electrolytes.

4. When the necessary doses of cortisone, DCA, and NaCl are known it may be desirable to implant pellets of DCA before discharging the child from the hospital. With the use of DCA there is less necessity for maintaining a constant high intake of NaCl, which may be difficult during acute illnesses when there is loss of appetite and vomiting.

In the four cases which we have treated the therapy shown in Table III has maintained the patients in health over periods of twenty to twenty-five months. It should be emphasized, however, that treatment must be properly adjusted to the particular needs of each patient. During the period of adjustment this requires very numerous and frequent determinations of the urinary 17-ketosteroids and the serum electrolytes.[15]

Does Prolonged Cortisone Therapy Permanently Alter the Adrenal Activity? When cortisone has been given intramuscularly for only a short period its withdrawal results in a rise of 17-ketosteroids beginning after ten to twelve days and a return to their former high level in two to three weeks (see Fig. 2). The withdrawal of oral cortisone causes a sharp rise within one to two days. Omission of cortisone was tried in an infant on the 227th day and later on the 280th day of therapy. In each instance the urinary 17-ketosteroids rose promptly to the pretreatment level or higher, suggesting that there had been no alteration in the adrenals. Subsequently we have

tried withdrawal of therapy in five older patients who had been treated continuously for periods of eight to twenty-four and one-half months. After discontinuing treatment for periods of seven to twenty-one days in order to determine the level to which the urinary 17-ketosteroids would rise, the patients were given ACTH 25 mg. q. 6 h. for periods of three or four days. The results are shown in Table IV and Fig. 6. Although there were moderate rises of the 17-ketosteroids, in no instance did the levels of excretion approach those which had existed before treatment. Following the test with ACTH the patients were allowed to continue without treatment for periods varying from fifteen to ninety days. In patient *J. St.* omission of therapy

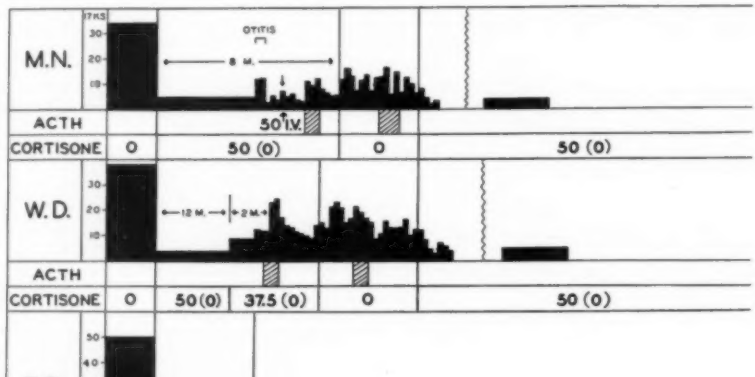

Fig. 6.—Chart shows effects on 17-ketosteroid excretion of withdrawing cortisone therapy and of administering ACTH in five female pseudohermaphrodites who had been treated continuously with cortisone for periods of eight to twenty-four and a half months. The first column shows average level of urinary ketosteroids before treatment, the second the average level during cortisone therapy. The following sections show the daily outputs of urinary ketosteroids during the withdrawal experiment. The ACTH tests indicated by the crossed-hatched areas consisted of administering intramuscular ACTH, 25 mg. q. 6 h. for three or four days.

for sixty days resulted in a rise of 17-ketosteroids to an average of 18.6 mg. per day (range 15.1 to 24.1) compared to a pretreatment level of 53 mg. per day. The hypertension which had existed before treatment recurred. In patient *M. Be.* the urinary 17-ketosteroids reached only 13.1 mg. per day after ninety days compared to 38 mg. per day before treatment. It cannot be stated whether withholding therapy for longer periods might eventually have resulted in a return of the previous level of adrenal hyperactivity.

TABLE IV

CASE NO.	CORTISONE TREATMENT (MG.) MAINTENANCE	DURATION (MO.)	17-KETOSTEROID EXCRETION—MG. PER DAY BEFORE RX	ON RX	WITH ACTH ON RX	OFF RX	WITH ACTH OFF RX	SUBSEQUENT OFF RX	CORTISONE RESUMED	TOTAL DURATION OF WITHDRAWAL DAYS
4. M. No.	50 oral	8	34	4.8	10.8		12.2	10.6	3.8	15
5. W. De.	50 oral	12	38	4.0						
	37.5	2 } 14		8.6	24.1	17.6	19.1	12.8	5.5	20
1. J. St.	25 i.m. 100 q.4 d.	24½	53	4.9		3.8	20	18.6		60
3. P. Ro.	Cort. 75 (o) F 75 (o)	20	50	5.6		9.6	15.1	11.1		45
6. M. Be.	25 i.m. 100 q.4 d.	24	38	4.4		8.9	17.4 ave. 22.7 max.	13.2	4.2	90

At least the findings indicate that long-continued treatment with cortisone caused a suppression of adrenal activity which persisted to some degree after its withdrawal. This offers the hope that perhaps after still longer periods of treatment, the adrenal disorder may be permanently altered and a relapse may not occur. This would be comparable to the results obtained with thiouracil drugs in some cases of hyperthyroidism.

SUMMARY

Female pseudohermaphroditism due to congenital adrenal hyperplasia must be distinguished from certain types of genetic intersexuality. Postnatal virilization of females due to adrenal tumor or hyperplasia must be differentiated from "premature pubarche," constitutional types of hirsutism, and arrhenoblastoma. Macrogenitosomia praecox due to adrenal hyperplasia or tumor in males must be differentiated from sexual precocity of constitutional type or due to an intracranial lesion. The diagnosis of the adrenogenital syndrome depends upon the demonstration of a high output of urinary 17-ketosteroids and clinical manifestations of excessive secretion of adrenal androgen. Adrenal hyperplasia can be distinguished from adrenal tumor by the fact that the administration of cortisone causes marked decrease in the output of 17-ketosteroids in cases of hyperplasia but not in those due to tumor.

Treatment with relatively small doses of cortisone is effective in suppressing the excessive secretion of adrenal androgen without causing abnormal metabolic or toxic effects. The minimum maintenance dose of intramuscular or oral cortisone must be determined in each case, following the urinary 17-ketosteroids and the rates of somatic growth and development as guides. In individuals of either sex

who have reached a level of somatic development comparable to that of puberty (i.e., a bone age of 11 years or greater) suppression of the adrenal hyperactivity with cortisone results promptly in normal adolescent sexual development corresponding to the sex of the patient. In more immature individuals progressive virilization is checked and precocious sexual development may not occur. With proper doses of cortisone somatic growth and development proceed normally. Excessive doses may inhibit them. The hypertension which occurs in some cases of adrenal hyperplasia is controlled by cortisone. In infants with congenital adrenal hyperplasia who have defective electrolyte metabolism, suppression of the abnormal adrenal hyperactivity with cortisone has a tendency to prevent Na loss so that smaller amounts of DCA and NaCl are required to regulate the electrolytes. After treatment with cortisone for one or two years, its omission for two or three months permits a partial return of the adrenal hyperactivity, but the 17-ketosteroids do not increase to as high a level as before treatment.

REFERENCES

1. Wilkins, L.: Hyperadrenocorticism, Pediatrics **3**: 533, 1949 The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., 1950, Charles C Thomas, chap. XIII.
2. Wilkins, L., Fleischmann, W., and Howard, J. E.: Macrogenitosomia Precox Associated With Hyperplasia of the Androgenic Tissue of Adrenal and Death From Corticoadrenal Insufficiency, Endocrinology **26**: 385, 1940.
3. Kyle, L. H., and Knop, C. Q.: Simulation of Cardiac Disease by Adrenocortical Failure in Infants, New England J. Med. **243**: 681, 1950.
4. Shepard, T. H., II, and Clausen, S. W.: Case of Adrenogenital Syndrome With Hypertension Treated With Cortisone, Pediatrics **8**: 805, 1951.
5. Wilkins, L., Crigler, J. F., Jr., Silverman, S. H., Gardner, L. I., and Migeon, C. J.: Further Studies on the Treatment of Congenital Adrenal Hyperplasia With Cortisone. III. The Control of Hypertension With Cortisone, With a Discussion of Variations in the Type of Congenital Adrenal Hyperplasia and Report of a Case With Probable Defect of Carbohydrate-regulating Hormones, J. Clin. Endocrinol. & Metab. **12**: 1015, 1952.
6. White, F. P., and Sutton, L. E.: Adrenogenital Syndrome With Associated Episodes of Hypoglycemia, J. Clin. Endocrinol. **11**: 1395, 1951.
7. Silverman, S. H., Migeon, C. J., Rosemberg, E., and Wilkins, L.: Precocious Growth of Sexual Hair Without Other Secondary Sexual Development. "Premature Pubarche," a Constitutional Variation of Adolescence, Pediatrics **10**: 426, 1952.
8. Gardner, L. I., and Migeon, C. J.: Le Diagnostic des Tumeurs Virilisantes du Cortex Surrenalien, Helvet. paediat. acta **6**: 466, 1952.
9. Venning, E.: Comments in Proc. of the Second ACTH Conference, John R. Mote, ed., Chicago, 1951, The Blakiston Co., pp. 91-92.
10. Gardner, L. I., Migeon, C. J., Crigler, J. F., Jr., Silverman, S. H., and Wilkins, L.: Urinary Dehydroisoandrosterone in Hyperadrenocorticism: Influences of Cortisone, Hydrocortisone and ACTH, J. Clin. Endocrinol. & Metab. (in press).
11. Sobel, E. H., Sniffen, R. C., and Talbot, N. B.: The Use of Testicular Biopsies in the Differential Diagnosis of Precocious Puberty, Pediatrics **8**: 701, 1951.
12. Wilkins, L., Lewis, R. A., Klein, R., and Rosemberg, E.: The Suppression of Androgen Secretion by Cortisone in a Case of Congenital Adrenal Hyperplasia, Bull. Johns Hopkins Hosp. **86**: 249, 1950.
13. Wilkins, L., Gardner, L. I., Crigler, J. F., Jr., Silverman, S. H., and Migeon, C. J.: Further Studies on the Treatment of Congenital Adrenal Hyperplasia With Cortisone. I. Comparison of Oral and Intramuscular Administration of Cortisone, With a Note on the Suppressive Action of Compounds F and B on the Adrenal, J. Clin. Endocrinol. & Metab. **12**: 257, 1952.
14. Ibid: II. The Effects of Cortisone on Sexual and Somatic Development, With an Hypothesis Concerning the Mechanism of Feminization, J. Clin. Endocrinol. & Metab. **12**: 277, 1952.
15. Crigler, J. F., Jr., Silverman, S. H., and Wilkins, L.: Further Studies on the Treatment of Congenital Adrenal Hyperplasia With Cortisone. IV. Effect of Cortisone and Compound B in Infants With Disturbed Electrolyte Metabolism, Pediatrics **10**: 397, 1952.

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Current Pediatric References

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Abdominal Pain 7074. Thomas, M. E. M.: "Epidemic" abdominal colic associated with steatorrhoea, Brit. M. J. **1**: 691-692, Mar. 29, 1952.

7075. Maldague, L.: La pathogénie des coliques ombilicales récidivantes des enfants, Acta paediat. belg. **6**: 53-60, No. 2, 1952.

Abscess, Leg 7076. Potts, F. N., & Rogers, Wm. J.: Foreign body simulating chronic osteomyelitis, New York J. Med. **52**: 1050, Apr. 15, 1952.

Abscess, Scalp 7077. MacCarthy, D., et al.: Scalp abscesses in the newborn, J. Obst. & Gynaec. Brit. Emp. **59**: 37-44, Feb., 1952.

Accidents 7078. Dettling, J.: Der Unfalltod im Kindesalter, speciell im motorisierten Strassenverkehr, Schweiz. med. Wchnschr. **82**: 377-379, Apr. 12, 1952.

Accidents, Eye 7079. LeWin, T.: Teaspoon penetrating child's orbit Arch Ophth. **47**: 515, Apr., 1952.

Acrocephalosyndactyly. See No. 7145.

ACTH 7080. Brody, S.: Psychiatric observations in patients treated with cortisone and ACTH, Psychosom. Med. **14**: 94-103, Mar.-Apr., 1952.

7081. Hailman, H. F.: ACTH and cortisone vs. salicylates, J. Clin. Endocrinol. **12**: 454-457, Apr., 1952.

7082. Hopkins, J. G., et al.: Pituitary adrenocorticotropic hormone (ACTH) and cortisone in diseases of the skin. 2. Allergic and other dermatoses; report of 67 cases, Arch. Dermat. & Syph. **65**: 401-421, Apr., 1952.

7083. Butterfield, W. J. H., et al.: Effect of adrenocorticotropic hormone on the survival of homografts, Acta haemat. **1**: 737-741, Apr. 12, 1952.

See Nos. 7116, 7154, 7184, 7251 and 7333.

Adrenal 7084. Rominger, E.: Zur prüfung der Funktionstüchtigkeit der Nebennierenrinde im frühen Kindesalter, Schweiz. med. Wchnschr. **82**: 411-413, Apr. 12, 1952.

7085. Ferrazzini, F., et al.: Funktionsprüfung der kindlichen Nebennierenrinde im 48-Stunden-test mit adrenocorticotropem Hormon, Helvet. paediat. acta **7**: 60-69, No. 1, 1952.

Adrenal Hyperplasia 7086. Rose, E. K., et al.: Adrenal cortical hyperfunction in childhood. Report of a case with adrenocortical hyperplasia and testicular adrenal rests, Pediatrics **9**: 475-484, Apr., 1952.

Allergy 7087. Sternberg, T. H., & Zimmerman, M. C.: Stress studies in the eczema-asthma-hay-fever diathesis, Arch. Dermat. & Syph. **65**: 392-400, Apr., 1952.

7088. Rocha E. Silva, M.: Concerning the mechanism of anaphylaxis and allergy, Brit. M. J. **1**: 779-787, Apr. 12, 1952.

Allergy. Egg 7089. Ratner, B., et al.: Allergy to viral and rickettsial vaccines. 3. Influence of repeated inoculations on the acquisition of egg allergy, New England J. Med. **246**: 533-536, Apr. 3, 1952.

Allergy, G. I. Tract 7090. Buffard, P., & Crozet, L.: Zur Dünndarmallergie, Fortschr. Geb. Röntgenstrahlen **76**: 497-507, Apr., 1952.

Allergy, Vaccine 7091. Ratner, B., et al.: Allergy to viral and rickettsial vaccines. 2. Allergic reactions encountered and further studies with refined influenza and mumps vaccines in allergic children, Am. J. Dis. Child, **83**: 608-617, May, 1952.

Anemia, Mediterranean 7092. Caminopetros, J.: The sickle-cell anomaly as a sign of Mediterranean anemia, Lancet **1**: 687-693, Apr. 5, 1952.

7093. Maléki, A.: Le diagnostic radiologique d'un cas d'anémie érythroblastique, J. radiol. et électrol. **33**: 152-153, No. 3-4, 1952.

Anemia, Megaloblastic 7094. Symposium: Megaloblastic anemia: current status of folic acid and vitamins B_{12} and C; Report of the 1st M & R Pediatric Research Conference, pp. 1-9.

Anemia, Sickle-Cell 7095. Neel, J. V.: Perspectives in the genetics of sickle cell disease, Blood **7**: 467-471, Apr., 1952.

7096. Jelliffe, D. B.: Sickle-cell disease, Tr. Roy. Soc. Trop. Med. & Hyg. **46**: 169-184, Mar., 1952.

7097. Peluffo, E., and Nordmann, J.: Sobre dos casos de anemia con celulas falciformes, Arch. pediat. Uruguay **23**: 37-41, Jan., 1952.

Aneurysm, Dissecting 7098. Case Report—dissecting aneurysm in a boy, Holzer Clinic Bull. **2**: 47-50, May, 1952.

Anomalies 7099. Murakami, U., et al.: A pedigree having hemophilia and color-blindness, and crossing-over of the two genes, Nagoya J. M. Sc. **14**: 58-61, July, 1951.

7100. Barter, R. H.: Dystocia due to fetal abnormalities, M. Ann. District of Columbia **21**: 181-186, Apr., 1952.

7101. Farias, J. G.: Consideraciones sobre un caso de paperas en el embarazo y malformaciones multiples en el hijo, Arch. pediat. Uruguay **23**: 42-44, Jan., 1952.

Anomalies, Esophagus 7102. Proux, Ch., & Hummel, J. A.: Les signes radiologiques du brachyoesophage et de la hernie diaphragmatique chez le nourrisson, Semaine Hôp. Paris **28**: 1131-1135, Apr. 10, 1952.

Anomalies, G. I. Tract. See No. 7165.

Anomalies, Tracheocholedochal 7103. Neuhauser, E. B. D., et al.: Congenital direct communication between biliary system and respiratory tract, Am. J. Dis. Child. **83**: 654-659, May, 1952.

Anomalies, Twinning 7104. Garry, T. P., & Solomons, E.: Thoracopagus. Report of a case with obstetrical and anatomical details and some embryological references, J. Obst. & Gynaec. Brit. Emp. **59**: 45-51, Feb., 1952.

Antibiotics 7105. Gould, J. C., & Bowie, J. H.: The determination of bacterial sensitivity to antibiotics, Edinburgh M. J. **59**: 178-199, Apr., 1952.

Antihistaminics 7106. Loew, E. R.: Pharmacological properties of antihistaminics in relation to allergic and non-allergic diseases, Boston Med. Quart. **3**: 1-6, Mar., 1952.

Apnoea (Swallow-Reflex) 7107. Willi, H., & Lüthy, F.: Schluckapnoe, Schweiz. med. Wchnschr. **82**: 397-399, Apr. 12, 1952.

Appendicitis 7108. Gibson, F.: Comments on acute appendicitis of childhood, M. J. Australia **1**: 369-370, Mar. 15, 1952.

Asphyxia Neonatorum 7109. Usdin, G. L., & Weil, M. L.: Effect of apnea neonatorum on intellectual development, Pediatrics **9**: 387-394, Apr., 1952.

Aspiration Pneumonia, Petroleum 7110. Nassau, E.: Ueber die Behandlung der Aspiration von Petroleum mit Cortison, Ann. Paediat. **178**: 181-184, Mar., 1952.

Atelectasis 7111. Barani, J. C.: Obstruccion bronquial por secreciones en un niño, Arch. pediat. Uruguay **23**: 45, Jan., 1952.

Aureomycin 7112. Garrahan, J. P., et al.: Aureomicina en pediatria. Nuestra experiencia, Arch. pediat. Uruguay **23**: 131-132, Feb., 1952.
See No. 7262.

Autism 7113. van Krevelen, D. A.: Early infantile autism, Ztschr. Kinderpsychiat. **19**: 91-97, Apr., 1952.

Bile Duct. Atresia 7114. Knorre, J.: Zur Kenntnis der angeborenen Atresie der Gallenwege, Bruns' Beitr. klin. Chir. **184**: 85-90, No. 1, 1952.

Bladder, Exstrophy 7115. Boyce, Wm. H., & Vest, S. A.: A new concept concerning treatment of exstrophy of the bladder, J. Urol. **67**: 503-517, Apr., 1952.

Blood Disease 7116. Heilmeyer, L.: ACTH and Cortisontherapie bei nichtleukämischen Bluterkrankungen, Acta haemat. **7**: 206-216, Apr., 1952.

Blood, Hemoglobins 7117. Chernoff, A. I., & Singer, K.: Studies on abnormal hemoglobins. 4. Persistence of fetal hemoglobin in the erythrocytes of normal children, Pediatrics **9**: 469-474, Apr., 1952.

Blood Platelets, Transfusion 7118. Hirsch, E. O.: The transfusion of human blood platelets, J. Lab. & Clin. Med. **39**: 556-569, Apr., 1952.

Blood Pressure 7119. Clayton, G. W., & Hughes, J. G.: Variations in blood pressure in hospitalized children, J. Pediat. **40**: 462-468, Apr., 1952.

Brain, Abscess of. See No. 7220.

Brain, Thrombosis of. See No. 7220.

Breast Feeding 7120. Kimball, E. R.: Breast feeding in private practice, Am. J. Dis. Child. **83**: 511-513, Apr., 1952.

7121. Stabile, A., & Bauza, C. A.: Causas de destete en el primer trimestre en lactantes de bajo nivel socio-economico, Arch. pediat. Uruguay **23:** 30-36, Jan., 1952.

Breast Milk 7122. Neuweiler, W.: Der Eisengehalt der Frauenmilch und seine Beeinflussung durch Eisenzufuhr, Schweiz. med. Wchnschr. **82:** 396-397, Apr. 12, 1952.

Bronchiectasis 7123. Currence, Wm. W.: Acetic acid aerosol in treatment of purulent bronchiectasis due to Pseudomonas aeruginosa, Am. J. Dis. Child. **83:** 637-641, May, 1952.

See No. 7246.

Bronchitis, Chronic 7124. Wissler, H.: Die chronische Bronchitis des Kindes, Schweiz. med. Wchnschr. **82:** 413-415, Apr. 12, 1952.

Calcinosis. See No. 7280.

Carbohydrate Metabolism 7125. Symposium —Carbohydrate metabolism, Report of 3rd M & R Pediatric Research Conference, pp. 9-23.

Carbonic Anhydrase 7126. Berfenstam, R.: Studies on carbonic anhydrase activity in children. 1. Enzyme Activity in the blood of infants and children of different ages, particularly in premature infants, Acta paediat. **41:** 32-52, Jan., 1952.

Cataract. See No. 7155.

Celiac Disease 7127. Anderson, C. M., et al.: Coeliac disease: gastro-intestinal studies and the effect of dietary wheat flour, Lancet **1:** 836-842, Apr. 26, 1952.

Cerebral Palsy 7128. Hicks, S. P.: 2. Some effects of ionizing radiation and metabolic inhibition on the developing mammalian nervous system, J. Pediat. **40:** 489-513, Apr., 1952.

7129. Palmer, M. F.: Speech therapy in cerebral palsy, J. Pediat. **40:** 514-524, Apr., 1952.

7130. Perlstein, M. A., & Barnett, H. E.: Nature and recognition of cerebral palsy in infancy, J.A.M.A. **148:** 1389-1397, Apr. 19, 1952.

7131. Perlstein, M. A.: Infantile cerebral palsy, J. A. M. A. **149:** 30-34, May 3, 1952.

7132. Strauss, A. A.: The education of the brain-injured child, Am. J. Ment. Deficiency **56:** 712-718, Apr., 1952.

Cerebrospinal Fluid 7133. Dubois, R.: Observations sur la glycorachie, Schweiz. med. Wchnschr. **82:** 401-403, Apr. 12, 1952.

Child Health 7134. Wright, F. H.: Well baby care, Texas Rep. Biol. & Med. **10:** 130-142, Spring, 1952.

Chloromycetin 7135. Thomas, J. W., et al.: Chloromycetin palmitate—clinical evaluation in allergic and non-allergic children and adults, Virginia M. Monthly **79:** 272-274, May, 1952.

7136. Ross, S., et al.: The use of Chloromycetin palmitate in infants and children: a preliminary report, Antibiotics & Chemotherapy **2:** 199-207, Apr., 1952.

Chondro-osteo-dystrophy 7137. Brailsford, J. F.: Chondro-osteo-dystrophy, J. Bone & Joint Surg. **34-B:** 56-63, Feb., 1952.

Circulation Time. See No. 7286.

Clubfoot 7138. Critchley, J. E., & Taylor, R. G.: Transfer of the tibialis anterior tendon for relapsed club-foot, J. Bone & Joint Surg. **34-B:** 49-52, Feb., 1952.

Colic, Umbilical. See No. 7075.

Color Blindness. See No. 7099.

Constipation 7139. Berger, H.: Das grosse atonische Colon bei gewissen Obstipationsformen der Kinder und seine Behandlung mit Sympathiocolytica, Ann. paediat. **178:** 187-206, Apr., 1952.

Convalescent Child 7140. Falkner, F.: The convalescent child, Lancet **1:** 657-659, Mar. 29, 1952.

Convulsions 7141. Lenggenhager, K.: Zur Genese der Fieberkrämpfe im Kindesalter, Schweiz. med. Wchnschr. **82:** 390-392, Apr. 12, 1952.

Cortical Hyperostosis 7142. Matheson, W. J., & Markham, M.: Infantile cortical hyperostosis, Brit. M. J. **1:** 742-744, Apr. 5, 1952.

Cortisone. See Nos. 7110, 7116, and 7154.

Coxsackie Virus 7143. Keller, W., & Vivell, O.: Weitere Untersuchungen über das Vorkommen von Coxsackie-virus Infektionen in Deutschland, Klin. Wchnschr. **30:** 289-297, Apr. 1, 1952.

7144. Freudenberg, E., et al.: Kongenitale Infektion mit Coxsackie-virus, Ann. paediat. **178:** 150-161, Mar., 1952.

Craniofacial Dysostosis 7145. Pinkerton, O. D., & Pinkerton, F. J.: Hereditary cranio-facial dysplasis, Am. J. Ophth. **35:** 500-506, Apr., 1952.

Cryptorchidism 7146. Mimpriss, T. W.: Cryptorchidism, Brit. J. Urol. **24:** 23-25, Mar., 1952.

Cyclencephalia 7147. Zellweger, H.: Kasuistischer Beitrag zum Problem der Cyclencephalie, und des congenital single lateral Ventricle, Helvet. paediat. acta **7:** 98-104, No. 1, 1952.

Cyst, Brain 7148. Logue, V., & Till, K.: Posterior fossa dermoid cysts with special reference to intracranial infection, J. Neurol. Neurosurg. & Psychiat. **15**: 1-12, Feb., 1952.

Cyst, Intracerebral 7149. Palma, E. C.: Angiografia cerebral en el diagnostico del quiste hidatico intracraneano. Contribucion a su tratamiento quirurgico, Arch. pediat. Uruguay **23**: 18-29, Jan., 1952.

7150. Palma, E. C., et al: Quiste hidatico del cerebro. En un niño de 3 anõs. Tecnica operatoria y resultados, Arch. pediat. Uruguay **23**: 102-115, Feb., 1952.

Cyst, Intrathoracic 7151. Veeneklaas, G. M. H.: Pathogenesis of intrathoracic gastrogenic cysts, Am. J. Dis. Child. **83**: 500-507, Apr., 1952.

Cyst, Thyroglossal 7152. Johns, D.: Respiratory obstruction in early infancy: report of four cases due to suprahyoid thyroglossal cyst, Am. J. Dis. Child. **83**: 515, Apr., 1952.

Cystinosis 7153. Jeune, M., et al.: Un cas de syndrome de Debré-de Toni-Fanconi par cystinose, Pédiatrie **41**: 159-170, No. 2, 1952.

Deafness. See No. 7161.

Debré-de Toni-Fanconi Syndrome. See No. 7153.

Dermatitis, contact 7154. Falk, M. S., et al.: Preliminary and short reports—treatment of severe rhus dermatitis with corticotropin or cortisone, J. Invest. Dermat. **18**: 307-310, Apr., 1952.

Diabetes 7155. Marr, Wm. G.: Cataracts and retinopathy in Jeuvenile diabetics, Am. J. Ophth. **35**: 577-582, Apr., 1952.

7156. Joslin, E. P.: Two diabetic children, Pediatrics **9**: 502, Apr., 1952.

7157. Kloos, K.: Zur Pathologie der feten und neugeborenen diabetischer Mütter, Arch. Path. Anat. **321**: 177-227, No. 3, 1952.

Diarrhea 7158. Mushin, R.: The bacteriology of infectious diarrhoea, M. J. Australia **1**: 428-432, Mar. 29, 1952.

7159. Rubbo, S. D.: Epidemiology of infectious diarrhoea, M. J. Australia **1**: 425-428, Mar. 29, 1952.

7160. Kadison, E. R.: Treatment of infantile diarrhea with a new combination of antibiotics, Am. J. Dis. Child. **83**: 513-514, Apr., 1952.

Dihydrostreptomycin 7161. Naismith, J. T.: Deafness with use of dihydrostreptomycin in tuberculous meningitis, Brit. M. J. **1**: 796-800, Apr. 12, 1952.

Diphtheria 7162. Vahlquist, B. A., & Nordbring, F.: Studies on diphtheria. 6. The effect of diphtheria immunization of newborn prematures, Acta paediat. **41**: 53-56, Jan., 1952.

7163. Maitland, H. B., et al.: Diphtheria anti-gravis serum: Its action on experimental infection and in the treatment of patients, J. Hyg. **50**: 97-106, Mar., 1952.

7164. Van Oye, E.: Recherches sur la composition de la moelle osseuse chez les enfants. 5. Le myélogramme dans la dipthére, Rev. belge path. et méd. expér. **21**: 385-388, Jan., 1952.

Duplications, Alimentary Tract 7165. Gross, R. E., et al.: Duplications of the alimentary tract, Pediatrics **9**: 449-468, Apr., 1952.

Dyschondroplasia 7166. Huart, J., & Richard, J.: Un cas de dyschondroplasie d'Ollier, Acta paediat. belg. **6**: 88-96, No. 2, 1952.

Dysostosis, Cleidocranial 7167. Richard, J.: Dysostose cleido-crânienne, Acta paediat. belg. **6**: 79-87. No. 2, 1952.

Dysplasia, Epiphysial 7168. Waugh. W.: Dysplasia epiphysialis multiplex in three sisters, J. Bone & Joint Surg. **34-B**: 82-87, Feb., 1952.

Dystrophy, Adiposogenital 7169. Prader, A., & Zellweger, H.: Periodische, hypokaliämische Lähmungen mit Hyperelektrolytämie bei einem Fall von Dystrophia adiposogenitalis, Helvet. paediat. acta **7**: 42-59, No. 1, 1952.

Ebstein's Disease. See No. 7216.

Eczema. See No. 7295.

Egressin. See No. 7302.

Electroencephalography 7170. De Toni, G.: La nobstra esperienza su 350 esami elettroencefalografici esequiti nell'età infantile, Minerva med. **43**: 525-531, No. 22, 1952.

Encephalitis 7171. Radermecker, J., & Macken, J.: Aspects électroencéphalographiques et cliniques de la leucoencéphalite sclérosante subaiquë, Rev. neurol. **85**: 341-370, No. 5, 1951.

Endocarditis 7172. Selawry, O.: $CuCl_2$ Kristallisation bei einem Fall von Endocarditis, Ann. paediat. **178**: 223-228, Apr., 1952.

Endocarditis, Bacterial 7173. Bain, R. C., et al.: Bacterial endocarditis of the tricuspid valve in a 15-month-old infant, Proc. Staff Meet., Mayo Clin. **27**: 180-187, Apr. 23, 1952.

Endocrinology 7174. Dods, L.: Some aspects of paediatric endocrinology, M. J. Australia **1**: 241-248, Feb. 23, 1952.

Enteritis 7175. Opitz, H.: Durch Pathogene colirassen bedingte Enteritisepidemien bei Säulingen, Helvet. paediat. acta **7**: 1-13, Mar., 1952.

Enuresis 7176. Atlee, C. N.: The problem of enuresis in childhood, Med. Press. No. 5890, 292-295, Mar. 26, 1952.

7177. Bostock, J., & Shackleton, M.: The enuresis dyad, M. J. Australia **1**: 357-360, Mar. 15, 1952.

Eosinophilia, Extreme 7178. Silver, H. K., et al.: Extreme eosinophilia, increased blood heterophile-agglutination titer, and hyperglobulinemia, Am. J. Dis. Child. **83**: 649-653, May, 1952.

Epidermolysis 7179. Noojin, R. O., et al.: Genetic study of hereditary type of epidermolysis bullosa simplex, Arch. Dermat. & Syph. **65**: 477-483, Apr., 1952.

Epiglottitis 7180. Gasser, C.: Epiglottis phlegmonosa oedematiens acutissima, Schweiz. med. Wchnschr. **82**: 379-381, Apr. 12, 1952.

Epilepsy 7181. Toman, J. E. P., et al.: The search for new drugs against epilepsy, Texas Rep. Biol. & Med. **10**: 96-104, Spring, 1952.

7182. Butter, A. J. M.: Tridione compared with malidone in the treatment of petit mal, J. Neurol. Neurosurg. & Psychiat. **15**: 37-38, Feb., 1952.

7183. Davies-Eysenck, M.: Cognitive factors in epilepsy, J. Neurol. Neurosurg. & Psychiat. **15**: 39-44, Feb., 1952.

Erythema Multiforme 7184. Steigman, A. J., & Kelly, J. J.: ACTH in erythema multiforme exudativum major, Lancet **1**: 875, Apr. 26, 1952.

Erythroblastosis, Fetal 7185. Kelsall, G. A., & Vos, G. H.: The antibody titre in maternal and infant's serum as an indication for treatment in haemolytic disease of the newborn, M. J. Australia **1**: 349-356, Mar. 15, 1952.

Esotropia 7186. Urist, M. J.: Surgical treatment of esotropia with bilateral elevation in adduction, Arch. Ophth. **47**: 220-247, Feb., 1952.

Fat Tolerance 7187. Droese, W.: Ueber die Fettoleranz der Säuglinge, Ann. paediat. **178**: 238-263, Apr., 1952.

7188. Droese, W.: Ueber die Fettoleranz der Säuglinge. Klinisch-experimentelle Untersuchung des Gallensäuren und Lipasengehaltes im Duodenalsaft, Ann. paediat. **178**: 121-149, Mar., 1952.

Feeding 7189. Illingworth, R. S., & Stone, D. G. H.: Self-demand feeding in a maternity unit, Lancet **1**: 683-687, Apr. 5, 1952.

7190. Malyoth, G.: Fünfzig Jahre Budinsche Zahl, Schweiz. med. Wchnschr. **82**: 307-310, Mar. 22, 1952.

See No. 7318.

Fractures, Spontaneous 7191. Kugelmann, J.: Ueber symmetrische Spontanfrakturen unbekannter Genese Beim Säugling, Ann. paediat. **178**: 177-181, Mar., 1952.

Gangrene, Lower Extremities. See No. 7391.

Gargoylism 7192. Caffey, J.: Gargoylism (Hunter-Hurler disease, dysostosis multiplex, lipochondrodystrophy), Am. J. Roentgenol **67**: 715-731, May, 1952.

Glaucoma 7193. Troncoso, M. U.: Surgical treatment of congenital glaucoma, Am. J. Ophth. **35**: 463-468, Apr., 1952.

Glycogen Disease 7194. Holt, L. E., Jr.: Hepatic form of glycogen disease (von Gierke's disease), Pediatrics **9**: 496-498, Apr., 1952.

Growth 7195. De Toni, G.: Introduccion al estudio del crecimiento del niño, Arch. pediat. Uruguay **23**: 5-17, Jan., 1952.

7196. De Toni, G.: Los factores del crecimiento del niño, Arch. pediat. Uruguay **23**: 72-88, Feb., 1952.

7197. Bayley, N., & Pinneau, S. R.: Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards, J. Pediat. **40**: 423-441, Apr., 1952.

Hand-Schüller-Christian Syndrome 7198. El Gholmy, A. A., & El Sebai, B.: Hand-Schüller-Christian syndrome, Arch. Pediat. **69**: 108-115, Mar., 1952.

Head-banging 7199. FitzHerbert, J.: Some further observations on head-banging and allied behaviour, J. Ment. Sc. **98**: 330-333, Apr., 1952.

Heart, ECG 7200. Veasy, L. G., & Adams, F. H.: Unipolar lead electrocardiography in children, Pediatrics **9**: 395-409, Apr., 1952.

7201. Goodwin, J. F.: The electrocardiogram in normal children and in children with right ventricular hypertrophy, Brit. Heart J. **14**: 173-184, Apr., 1952.

Heart Disease, Congenital 7202. Deuchar, D. C., & Knebel, R.: The pulmonary and systemic circulations in congenital heart disease, Brit. Heart J. **14**: 225-249, Apr., 1952.

7203. Lurie, P. R., et al.: Cardiac catheterization and other physiological studies in fifty cases of congenital heart disease, Angiology **3**: 98-166, Apr., 1952.

7204. Cooley, R. N., & Sloan, R. D.: Angiocardiography in congenital heart disease of cyanotic type. 3. Observations on complete transposition of the great vessels, Radiology **58**: 481-506, Apr., 1952.

7205. Wenger, R., & Wiek, E.: Vektocardiographische untersuchungen bei angeborenen Anomalien des Herzens und der grossen Gefässe, Cardiologia **20**: 1-26, No. 1, 1952.

7206. Segers, M., et al.: Modifications intermittentes de l'image de preponderance dans les cardiopathies congenitales, Acta cardiol. **7**: 196-206, No. 2, 1952.

7207. Cherwitz, G.: A general clinical approach to acyanotic congenital heart disease, Chicago Med. School Quart. **13**: 120-125/129, Apr., 1952.

7208. Gasul, B. M., & Fell, E. H.: Diagnosis of the infantile type of coarctation of the aorta, Am. J. Dis. Child. **83**: 509-510, Apr., 1952.

7209. Larsen, K.: Coarctation of the aorta descendens, Acta med. scandinav. suppl. **266**: 661-670, 1952.

7210. Lubert, M., et al.: An unusual variant of double aortic arch, Am. J. Roentgenol. **67**: 763-776, May, 1952.

7211. Ziegler, R. F.: The importance of patent ductus arteriosus in infants, Am. Heart J. **43**: 553-572, Apr., 1952.

7212. Woods, A.: The electrocardiogram in the tetralogy of Fallot, Brit. Heart J. **14**: 193-203, Apr., 1952.

7213. Smull, N. W., & Lamb, L. E.: Interauricular septal defect, Am. Heart J. **43**: 481-493, Apr., 1952.

7214. Cahen, P., et al.: Faux syndrome de Lutembacher par persistance de l'ostium primum avec scission de la valve mitrale interne, Arch. mal. coeur. **45**: 203-219, Mar., 1952.

7215. Barnes, C. G., & Finlay, H. V. L.: Cor triatriatum, Brit. Heart J. **14**: 283-287, Apr., 1952.

7216. Grob, M., et al.: Zur Diagnose des Morbus Ebstein, Helvet. pediat. acta **7**: 85-97, No. 1, 1952.

7217. Potter, C. T., & Trounce, D. Q.: Congenital partial heart block, Brit. Heart J. **14**: 291-293, Apr., 1952.

7218. Freel, J. A.: The cardiac transition of the newborn. Congenital cardiac dilatation with heart block, Arch. Pediat. **69**: 116-135, Mar., 1952.

7219. Hanlon, C. R.: Present status of cardiovascular surgery, J.A.M.A. **149**: 1-7, May 3, 1952.

7220. Broager, B., & Hertz, H.: Cerebral complications in congenital heart disease, Acta med. scandinav. suppl. 266, 1952.

7221. Rosenbaum, F. F., & Stiles, F. C.: An unusual mechanism of sudden death in congenital heart disease, Am. Heart J. **43**: 573-581, Apr., 1952.

Hemangioma 7222. Brain, R. T., & Calnan, C. D.: Vascular naevi and their treatment, Brit. J. Dermat. **64**: 147-153, Apr., 1952.

Hemangioma, Scalp 7223. Wakeley, C.: Haemangioma of the scalp in a child, Med. Press No. 5891; 325, Apr. 2, 1952.

Hematoma, Subdural 7224. Bernheim, et al.: Hématomes sous-duraux consécutifs aux méningites suppurées, Pédiatrie **41**: 153-157, No. 2, 1952.

Hemophilia 7225. Quick, A. J., & Hussey, C. V.: Hemophilia: clinical and laboratory observations relative to diagnosis and inheritance, Am. J. M. Sc. **223**: 401-413, Apr., 1952.
See No. 7099.

Hepatitis. See No. 7231.

Hepatomegaly 7226. Garot, L.: Hépatomégalie et déficience de l'état géneral dans la moyenne enfance, Acta paediat. belg. **6**: 61-66, No. 2, 1952.

Hernia, Diaphragmatic. See No. 7102.

Hernia, Femoral 7227. Temple, J. L.: Strangulated femoral hernia in a young boy, Lancet **1**: 594, Mar. 22, 1952.

Hernia, Inguinal 7228. Iason, A. H.: Inguinal hernia in infants, GP **5**: 67-71, May, 1952.

7229. Heifetz, C. J.: Surgery for inguinal hernias in infancy and childhood, Am. J. Surg. **83**: 653-663, May, 1952.

Herpes Simplex 7230. Florman, A. L., & Midlin, R. W.: Generalized herpes simplex in an eleven-day-old premature infant, Am. J. Dis. Child. **83**: 481-486, Apr., 1952.

Herpes Simplex Virus 7231. Zuelzer, W. W., & Stulberg, C. S.: Herpes simplex virus as the cause of fulminating visceral disease and hepatitis in infancy, Am. J. Dis. Child. **83**: 421-439, 1952.

Herpetic Angina 7232. Schiff, E.: Angina Herpetica und Masern, Ann. paediat. **178**: 161-164, Mar., 1952.

Histoplasmosis 7233. Carpenter, A. M., & Spino, P. D.: Incidence of skin-test reactions among children in the Pittsburgh district. 1. Histoplasmin, Am. J. Dis. Child. **83**: 589-597, May, 1952.

Hydatid Cyst. See No. 7149 and No. 7150.

Hypoparathyroidism 7234. Simpson, J. A.: The neurological manifestations of idiopathic hypoparathyroidism, Brain **75**: 76-90, Mar., 1952.

Immunization 7235. Wishart, F. O., et al.: Diphtheria antitoxin titres following a recall dose of diphtheria toxoid, Canad. J. Pub. Health **43**: 121-127, Mar., 1952.

Incontinentia Pigmenti 7236. Loveman, A. B., et al.: Incontinentia pigmenti, J. Pediat. **40**: 442-450, Apr., 1952.

7237. Haber, H.: The Bloch-Sulzberger syndrome (incontinentia pigmenti), Brit. J. Dermat. **64**: 129-140, Apr., 1952.

7238. Findlay, G. H.: On the pathogenesis of incontinentia pigmenti. With observations on an associated eye disturbance resembling retrolental fibroplasia, Brit. J. Dermat. **64**: 141-146, Apr., 1952.

Influenza 7239. Dawson, B., & Zinnemann, K.: Incidence and type distribution of capsulated H. influenzae strains, Brit. M. J. **1**: 740-742, Apr. 5, 1952.

Intestine, Obstruction 7240. Bierman, C. W., et al.: Intestinal obstruction in a premature infant treated by resection and primary end-to-end anastomosis, J. Pediat. **40**: 474-478, Apr., 1952.

7241. Jaccotet, M.: Deux cas d'obstruction du duodénum, Schweiz. med. Wchnschr. **82**: 385-387, Apr. 12, 1952.

Intestine, Rotation 7242. Warthen, R. O., et al.: Reversed rotation of the bowel, Am. J. Dis. Child. **83**: 487-492, Apr., 1952.

Intussusception 7243. Schein, C. J., & Bluestone, L.: Jejunal intussusception in childhood due to tumor, Surgery **31**: 609-611, Apr., 1952.

7244. Ravitch, M. M., & Morgan, R. H.: Reduction of intussusception by barium enema, Ann. Surg. **135**: 596-605, May, 1952.

Kaposi's Varicelliform Eruption 7245. Selonim, M. H.: Kaposi's varicelliform eruption due to vaccinia virus, M. J. Australia **1**: 434-435, Mar. 29, 1952.

Kartagener's Syndrome 7246. Maher, R. J.: Kartagener's triad, Clin. Proc. Child. Hosp. Wash., D. C. **8**: 75-77 Apr., 1952.

Kidney, Calculi 7247. Clarke, H.: Report of a case with bilateral renal calculi in a child with normal kidneys, Brit. J. Urol. **24**: 56-57, Mar., 1952.

Kidney, Polycystic 7248. Robbins, S. L.: The association of "berry" aneurysms of the circle of Willis with congenital polycystic kidney disease, Boston Med. Quart. **3**: 7-10, Mar., 1952.

Laryngotracheobronchitis 7249. High, H. C., Jr.: The treatment of acute laryngotracheobronchitis, Wisconsin M. J. **51**: 367-370, Apr., 1952.

7250. Folken, F. G.: Acute larngotracheobronchitis, Minnesota Med. **35**: 336-339, Apr., 1952.

Laryngotracheitis 7251. Turner, J. A., & Morgan, E. A.: Corticotropin (ACTH) in the treatment of acute laryngotracheitis, Am. J. Dis. Child. **83**: 440-445, Apr., 1952.

Leukemia, Chronic Myelocytic 7252. Leiken, S., & Waters, R. J.: Chronic myelocytic-leukemia in childhood, Clin. Proc. Child. Hosp. Wash., D. C. **8**: 78-84, Apr., 1952.

Liver, Biopsy 7253. Silvera, W. D., & Jelliffe, D. B.: Liver biopsies in Nigerian children, J. Trop. Med. **55**: 73-79, Apr., 1952.

Liver Function 7254. Obrinsky, Wm., et al.: Sulfobromophthalein sodium excretion test as a measure of liver function and premature infants, Pediatrics **9**: 421-438, Apr., 1952.

Lobstein's Disease. See No. 7362.

Lymphogranuloma 7255. Banov, L., Jr.: Rectal lesions of lymphogranuloma venereum in childhood, Am. J. Dis. Child. **83**: 660-662, May, 1952.

Malnutrition 7256. Spies, T. D., et al.: Detection and treatment of nutritive failure in children, J.A.M.A. **148**: 1376-1382, Apr. 19, 1952.

Measles 7257. Van Oye, E.: Recherches sur la composition de la moelle osseuse chez les enfants. 3. Le myélogramme dans la rougeole, Rev. belge. path. et méd. expér. **21**: 377-380, Jan., 1952.

See No. 7232.

Meckel's Diverticulum 7258. Brown, K. L., & Glover, D. M.: Persistent omphalomesenteric duct, Am. J. Surg. **83**: 680-685, May, 1952.

Megacolon 7259. Jolleys, A.: Death following a barium enema in a child with Hirschsprung's disease, Brit. M. J. **1**: 692-693, Mar. 29, 1952.

7260. Leon, E. E., & Karshner, R. G.: Hirschsprung's disease and congenital megacolon, California Med. **76**: 276-280, Apr., 1952.

Melorheostosis 7261. Jeune, M., et al.: Mélorhéostose, Pédiatrie **41**: 222-224, No. 2, 1952.

Meningitis, Influenzal 7262. McGovern, J. M., et al.: Aureomycin in the treatment of influenzal meningitis, Clin. Proc. Child. Hosp. Wash., D. C. **8**: 69-75, Apr., 1952.

Meningitis, Leptospiral 7263. Beeson, P. B., & Hankey, D. D.: Leptospiral meningitis, Arch. Int. Med. **89:** 575-583, Apr., 1952.

Meningitis, Mixed Infection 7264. Van den Bosch, E.: Infection méningée mixte à pneumocoques et à bacille de Koch, Acta paediat. belg. **6:** 67-72, No. 2, 1952.

Meningitis, Pneumococcal 7265. Kahn, E., & Shnier, M. H.: Pneumococcal meningitis, South African M. J. **26:** 212-214, Mar. 15, 1952.

7266. Meyers, R. I.: Pneumococcal meningitis treated without intrathecal chemotherapy, M. J. Australia **1:** 295-297, Mar. 1, 1952.

Meningitis, Salmonella 7267. Feuillen, Y.-M., & Joiris, E.: Méningite à salmonella Brandenburg, Acta paediat. belg. **6:** 73-78, No. 2, 1952.

Meningitis, Tuberculous 7268. Harrison, H. E., et al.: Disturbances of ionic equilibrium of intracellular and extracellular electrolytes in patients with tuberculous meningitis, J. Clin. Investigation **31:** 300-308, Mar., 1952.

7269. Dubos, René J.: Discussion on treatment of tuberculous meningitis and survival of bacilli in tuberculous lesions, Am. Rev. Tuberc. **65:** 637-640, May, 1952.

7270. Schwarz, H.: Weitere Pathologisch-anatomische Untersuchungen Über die mit streptomycin und PAS behandelte Meningitis tuberculosa, Schweiz. Ztschr. Tuberk. **9:** 167-192, No. 3, 1952.

See No. 7161.

Meningocele, Thoracic 7271. Rubin, S., & Stratemeier, E. H.: Intrathoracic meningocele, Radiology **58:** 552-555, Apr., 1952.

Mental Deficiency 7272. Kirman, B. H.: Familial cataract and mental deficiency, Lancet **1:** 694-696, Apr. 5, 1952.

7273. Kirk, S. A.: Experiments in the early training of the mentally retarded, Am. J. Ment. Deficiency **56:** 692-700, Apr., 1952.

7274. Menzel, M. Z.: Psychotherapeutic techniques among the mentally deficient. Occupational therapy, Am. J. Ment. Deficiency **56:** 796-802, Apr., 1952.

7275. Smith, E. M.: Emotional factors as revealed in the intake process with parents of defective children, Am. J. Ment. Deficiency **56:** 806-812, Apr., 1952.

Mongolism 7276. Engler, M.: A comparative study of the causation of mongolism, peristatic amentia, and other types of mental defects, J. Ment. Sc. **98:** 316-325, Apr., 1952.

7277. Rothschild, I., & Riepenhoff, J. P.: The circulating eosinophil response to epinephrine in mongolism, J. Clin. Endocrinol. **12:** 480-482, Apr., 1952.

Morquio's Disease. See No. 7137.

Mortality, Infant 7278. Brooks, M. B., et al.: Premature infant mortality, Am. J. Dis. Child. **83:** 642-644, May, 1952.

Mutism 7279. Misch, A.: Elektiver Mutismus im Kindesalter, Ztschr. Kinderpsychiat. **19:** 49-87, Apr., 1952.

Myositis Ossificans 7280. Fontaine, René: A propos d'une observation decalcinose tumorale, très Améliorée par une thymoparathyroidectomie, avec étude du bilan calcique a minima, Semaine hôp. Paris **28:** 1211-1217, Apr. 18, 1952.

Neomycin. See No. 7293.

Nephritis 7281. Fanconi, G.: Von der Nosologischen zur funktionellen Betrachtungsweise der Nephropathien, Schweiz. med. Wchnschr. **82:** 404-407, Apr. 12, 1952.

Nephrosclerosis 7282. Fomon, S. J., et al.: Malignant nephrosclerosis without retinal edema in a child, Am. J. Dis. Child. **83:** 493-499, Apr., 1952.

Nephrosis 7283. Gairdner, D.: Nephrosis treated by malaria, Lancet **1:** 842-844, Apr. 26, 1952.

7284. Byrne, E. A. J.: Malarial therapy in lipoid nephrosis, Lancet **1:** 844-845, Apr. 26, 1952.

Neuroblastoma 7285. Hudson, H. W., et al.: Successful treatment of neuroblastoma, New England J. Med. **246:** 536-537, Apr. 3, 1952.

Newborn 7286. Lesser, R. E., et al.: Circulation times in newborn infants by the fluorescein method, Am. J. Dis. Child. **83:** 645-648, May, 1952.

See Nos. 7144, 7230, 7242, 7271, and 7369.

Newborn, Emergencies 7287. Ellis, R. W. B.: Paediatric emergencies, Practitioner **168:** 338-346, Apr., 1952.

Nutrition 7288. Irving, J., et al.: The biological value and true digestibility of the proteins contained in whitefish flour, the standard loaf and standard loaf supplemented by whitefish flour, South African M. J. **26:** 206-212, Mar. 15, 1952.

Oligophrenia 7289. Rudolf, G. de M.: The effect of sex hormones in oligophrenia, J. Ment. Sc. **98:** 294-298, Apr., 1952.

Ollier's Disease. See No. 7166.

Osteochondritis, Vertebral 7290. Hafner, R. H. V.: Localised osteochondritis (Scheuermann's disease), J. Bone & Joint Surg. **34-B:** 38-40, Feb., 1952.

Osteogenesis Imperfecta 7291. Basu, A. K., & Niyogi, S.: Osteogenesis imperfecta tarda, Indian M. Gaz. **86**: 487-489, Nov., 1951.

Osteomyelitis 7292. De Camargo, F. P., & Passarelli, J., Jr.: Osteomielite consequente a infusão intramedular em lactentes, Rev. Hosp. clin. **7**: 33-40, Jan., 1952.

Osteopetrosis (Leri). See No. 7261.

Otitis Media 7293. Lazar, A. M., et al.: Treatment of otitis media caused by Pseudomonas aeruginosa in infants with neomycin, Arch. Otolaryng. **55**: 444-450, Apr., 1952.

Pancreas, Functional Test 7294. De Muralt, G.: Un test de détection de la trypsine dans les belles, Helvet. paediat. acta **7**: 70-84, No. 1, 1952.

Panthenol 7295. Kline, P. R., & Caldwell, A.: Treatment of various dermatoses with topical application of panthenol, New York J. Med. **52**: 1141-1143, May 1, 1952.

Parkinsonism 7296. Farquhar, J. W.: Treatment of parkinsonism in a child, Lancet **1**: 638-640, Mar. 29, 1952.

Pellagra 7297. Flies, A.: Ueber einen Fall von infantiler Pellagra, Ann. paediat. **178**: 165-176, Mar., 1952.

Penicillin 7298. Lepper, M. H., et al.: Use of dibenzylethylenediamine penicillin administered orally in bacterial infections, Antibiotics & Chemotherapy **2**: 175-178, Apr., 1952.
See No. 7349.

Pertussis 7299. Ungar, J.: Recent advances in pertussis immunisation, Irish J. M. Sc. No. 316: 145-159, Apr., 1952.

7300. Van Oye, E.: Recherches sur la composition de la moelle osseuse chez les enfants. 2. Le myélogramme dans la coqueluche, Rev. belge. path. et méd. expér. **21**: 373-376, Jan. 1952.

Phenylketonuria. See No. 7289.

Phlebectasia, Congenital 7301. Humphries, J. M.: Generalized congenital phlebectasia, J. Pediat. **40**: 486-488, Apr., 1952.

Pinworms 7302. Goddard, R. F., & Brown, H. W.: The treatment of pinworm infection (enterobius vermicularis) with Egressin, J. Pediat. **40**: 469-473, Apr., 1952.

Pneumonia 7303. Engel, S.: Zur Lokalisation der lobären Pneumonie im Kindesalter, Schweiz. med. Wchnschr. **82**: 403-404, Apr. 12, 1952.

Pneumonia, Interstitial 7304. Wolman, M., et al.: Studies on interstitial giant cell pneumonia, Am. J. Dis. Child. **83**: 573-588, May, 1952.

7305. Hallauer, C.: Beitrag zur Virus ätiologie der frühinfantilen Interstitielle plasmarcellulären Pneumonie, Schweiz. med. Wchnschr. **82**: 409-411, Apr. 12, 1952.

Poisoning, Kerosene 7306. Olstad, R. B., & Lord, R. M., Jr.: Kerosene intoxication, Am. J. Dis. Child. **83**: 446-453, Apr., 1952.

7307. Caussade, L., et al.: Pneumopathies par ingestion de pétrole, Pédiatrie **41**: 147-150, No. 2, 1952.

Poliomyelitis 7308. Smallpeice, V., & Ounsted, C.: Cerebral poliomyelitis in early infancy, J. Neurol. Neurosurg. & Psychiat. **15**: 13-19, Feb., 1952.

7309. Wright, G. A., & Owen, T. K.: Poliomyelitis in mother and newborn infant, Brit. M. J. **1**: 800-801, Apr. 12, 1952.

7310. Weinstein, L.: The influence of muscular fatigue, tonsillo-adenoidectomy and antigen injections on the clinical course of poliomyelitis, Boston Med. Quart. **3**: 11-16, Mar., 1952.

7311. Bengtsson, E., & Johnsson, T.: Electrocardiographic changes in acute anterior poliomyelitis. Cardiologia **20**: 65-80, No. 2, 1952.

7312. Raisman, V.: Orthopedic treatment of acute and subacute poliomyelitis with curare and stretching, New York J. Med. **52**: 1147-1149, May, 1952.

7313. Knuchel, P.: Die polioencephalitische Verlaufsform der epidemischen Kinderlähmung, Schweiz. med. Wchnschr. **82**: 388-390, Apr. 12, 1952.

7314. Boyer, J.: Épidémiologie et prophylaxie de la policmyélite, Semaine Hôp. Paris **28**: 1263-1271, Apr. 22, 1952.

Prematurity 7315. Holmdahl, K.: The programme for premature infants in Gothenburg, Sweden. The principles of treatment and the results obtained, Acta paediat. **41**: 1-14, Jan., 1952.

7316. Crump, E. P., et al.: Prematurity in the Negro infant, Am. J. Dis. Child **83**: 463-474, Apr., 1952.

7317. Wallace, H. M., et al.: Report of two years' experience in the transportation of premature infants in New York City, Pediatrics **9**: 439-448, Apr., 1952.

7318. Andelman, M. B., et al.: Effects of early feeding of strained meat to prematurely born infants, Pediatrics **9**: 485-491, Apr., 1952.

7319. Cross, K. W., & Oppé, T. E.: The respiratory rate and volume in the premature infant, J. Physiol. **116**: 168-174, Feb. 28, 1952.
See Nos. 7240, 7254, 7278, and 7329.

Prolapse, Sigmoid Colon 7320. Babich, J. M., et al.: Internal prolapse of sigmoid colon in infants and children, J. Pediat. **40**: 479-481, Apr., 1952.

Pseudohermaphroditism 7321. Excretion of estrogens and a metabolite in the urine of female pseudohermaphrodites, Endocrinology **50:** 271-272, Feb., 1952.

Psychiatry 7322. Sager, C. J.: The concept of aggression in modern psychiatry, Ment. Hyg. **36:** 210-219, Apr., 1952.

Psychopathology 7323. Stouffer, G. A. W., Jr.: Behavior problems of children as viewed by teachers and mental hygienists, Ment. Hyg. **36:** 371-385, Apr., 1952.

Purpura 7324. Kost, F.: Zum Problem der Purpura fulminans, Ann. paediat. **178:** 228-237, Apr., 1952.

Pyelitis 7325. Ney, C., & Markham, M. J.: The importance of examining the lower uninary tract in so-called pyelitis of children, New York J. Med. **52:** 1033-1037, Apr. 15, 1952.

Pyelography 7326. Hodge, K. E.: Intramuscular pyelography in children, Brit. J. Radiol. **25:** 209, Apr., 1952.

Resuscitation. See No. 7287.

Reticuloendotheliosis 7327. Nelson, R. A., & Stofer, B. E.: Acute reticuloendotheliosis (Letterer-Siwe disease), Am. J. Dis. Child. **83:** 475-480, Apr., 1952.

Retrolental Fibroplasia 7328. Bjelkhagen, I.: Retrolental Fibroplasia in Sweden, Acta paediat. **41:** 74-86, Jan., 1952.

7329. Hipsley, E. H.: The incidence of retrolental fibroplasia in premature infants in Sydney, M. J. Australia **1:** 473-475, Apr. 5, 1952.

7330. Bembridge, B. A., et al.: Retrolental fibroplasia, Brit. M. J. **1:** 675-679, Mar. 29, 1952.

7331. Symposium—Retrolental Fibroplasia, 2nd M & R Pediatric Research Conference, pp. 8-58.

7332. Goldmann, H., & Tobler, W.: Zur Aetiologie der retrolentalen Fibroplasie, Schweiz. med. Wchnschr. **82:** 381-385, Apr. 12, 1952.

Rheumatic Diseases 7333. Brøchner-Mortensen, K.: Treatment of rheumatic fever with ACTH (cortrophin), Acta med. scandinav. suppl. **266:** 299-313, 1952.

7334. Griffith, G. C., & Scheinkopf, J. A.: Diagnosis and differential diagnosis of rheumatic fever, Acta med. scandinav. suppl. **266:** 429-438, 1952.

7335. LeBus, H. E., & Panos, T. C.: A study of ninety-one children with rheumatic fever in the Gulf coast area of Texas, Texas Rep. Biol. & Med. **10:** 45-52, Spring, 1952.

7336. Finkel, S., & Baldwin, J. S.: Q-T interval during active and inactive rheumatic fever, Pediatrics **9:** 410-420, Apr., 1952.

7337. Hansen, A. E.: Importance of early diagnosis in acute rheumatic fever, J. A. M. A. **148:** 1481-1485, Apr. 26, 1952.

7338. Symposium—present state of knowledge concerning pathogenesis and treatment of rheumatic fever. Bull. New York Acad. Med. **28:** 307-334, May, 1952.

7339. Kelley, V. C.: Acute phase reactants. 1. Serum nonglucosamine polysaccharides in patients with rheumatic fever and related conditions, J. Pediat. **40:** 405-412, Apr., 1952.

7340. Kelley, V. C.: Acute phase reactants. 2. Serum hexosamines in patients with rheumatic fever and related diseases, J. Pediat. **40:** 413-422, Apr., 1952.

7341. Lewy, F. J.: Diagnostic problems of rheumatic fever and their impact on the management of the rheumatic fever patient, Ann. Int. Med. **36:** 1042-1049, Apr., 1952.

7342. Simon, A. J., et al.: Accelerated rehabilitation in rheumatic fever, Am. J. Dis. Child. **83:** 454-462, Apr., 1952.

Rheumatoid Arthritis 7343. Bernheim, M., et al.: Le syndrome de Wissler-Fanconi. (Discussion étio-pathogénique), Pédiatrie **41:** 229-234, No. 2, 1952.

Rickets, Vitamin D Resistant 7344. Fanconi, G., & Girardet, P.: Familiärer persistierender Phosphatdiabetes mit D-vitamin-resistenter Rachitis, Helvet. paediat. acta **7:** 14-41, No. 1, 1952.

Ringworm, Scalp 7345. Price, H., & Taylor, D. R.: Trichophyton tonsurans (crateriforme) infection of the scalp, California Med. **76:** 283-288, Apr., 1952.

Ritter's Disease 7346. Klenerman, P.: Ritter's disease and sclerema, South African M. J. **26:** 260-262, Mar. 29, 1952.

Rocky Mountain Fever 7347. Bow, M. R., & Brown, J. H.: Rocky Mountain spotted fever in Alberta, 1935-1950, Canad. J. Pub. Health **43:** 109-115, Mar., 1952.

Rubella 7348. Korns, R. F.: Prophylaxis of German measles with immune serum globulin, J. Infect. Dis. **90:** 183-189, Mar.-Apr., 1952.

Salicylates. See No. 7081.

Scarlet Fever 7349. Mathieu, P. L., Jr., et al.: Scarlet fever. Evaluation of continuous and intermittent-penicillin therapy, Am. J. Dis. Child. **83:** 628-636, May, 1952.

7350. Van Oye, E.: Recherches sur la composition de la moelle osseuse chez les enfants. 4. Le myélogramme dans la scarlatine Rev. belge path. et méd. expér. **21:** 381-384, Jan., 1952.

Scheuermann's Disease. See No. 7290.

Schizophrenia 7351. Eickhoff, L. F. W.: The aetiology of schizophrenia in childhood, J. Ment. Sc. **98**: 229-234, Apr., 1952.

Sclerema. See No. 7346.

Scleroderma 7352. Longacre, J. J., & Wagner, E. A.: The surgical management of disabling contractures due to linear scleroderma, Plast. & Reconstruct. Surg. **9**: 367-380, Apr., 1952.

Speech Disorder 7353. Wohlman, R. F.: The integrated treatment of a young child with a speech disorder, J. Pediat. **40**: 525-529, Apr., 1952.

Steatorrhoea. See No. 7074.

Strabismus 7354. Douglas, A. A.: Value of orthoptics in the treatment of squint, Brit. J. Ophth. **36**: 169-201, Apr., 1952.

Streptomycin. See Nos. 7372 and 7379.

Stridor. See No. 7363.

Syphilis 7355. Aron, H. C. S., et al.: Further observations on biologic false positive serologic tests in young children, Am. J. Syph. **36**: 278-283, May, 1952.

Teeth 7356. Clarke, G. K.: Dental care of the pre-school child, Canad. J. Pub. Health **43**: 116-120, Mar., 1952.

7357. Stafne, E. C.: Dental roentgenologic manifestations of systemic disease. 2. Developmental disturbances, Radiology **58**: 507-515, Apr., 1952.

7358. Ainsworth, N. J.: Modern trends in the prevention of dental caries in children, M. Press **227**: 386-390, Apr. 23, 1952.

7359. Hadjimarkos, D. M., et al.: Selenium and dental caries, J. Pediat. **40**: 451-455, Apr., 1952.

Testes 7360. Hansen, P. F., & With, T. K.: Clinical measurements of the testes in boys and men, Acta med. scandinav. suppl. **266**: 457-465, 1952.

Tetanus 7361. Sternberg. H. M., et al.: Tetanus in an epileptic, Arch. pediat. **69**: 101-107, Mar., 1952.

Thorn Puncture. See No. 7383.

Thrombasthenia 7362. Gautier, P., & Guinand-Doniol, Jr.: Un syndrome nouveau: La maladie de Lobstein associée à la thrombasthénie familiale et héréditarie de Glanzmann, Schweiz. med. Wchnschr. **82**: 407-409, Apr. 12, 1952.

Thymus 7363. Fermin, H., & Wilms, F. J.: Thymus and stridor, Pract. oto-rhino-laryng. **14**: 75-81, No. 2, 1952.

7364. Bétouliéres, P., & Paleirac, R.: Quelques aspects radiologiques de Thymus, J. radiol. et électrol. **33**: 167-174, No. 3-4, 1952.

7365. Paltrinieri, G.: La scoliose mégalothymique, J. radiol. et électrol. **33**: 30-34, No. 1-2, 1952.

Tibia, Kyphoscoliotic 7366. Badgley, C. E., et al.: Congenital kyphoscoliotic tibia, J. Bone & Joint Surg. **34A** 349-371/494, Apr., 1952.

Toxoplasmosis 7367. Gard, S.. et al.: Congenital toxoplasmosis, Acta paediat. **41**: 15-31, Jan., 1952.

Toxoplasmosis 7368. Bamatter, F., & Habegger, H.: La toxoplasmose en neurologie humaine, Schweiz. med. Wchnschr. **82**: 372-375, Apr. 12, 1952.

Trachea 7369. Donaldson, S. W., & Tompsett, A. C., Jr.: Tracheal diameter in the normal newborn infant, Am. J. Roentgenol. **67**: 785-787, May, 1952.

Tuberculin Tests 7370. Carpenter, A. M., et al.: Incidence of skin-test reactions among children in the Pittsburgh district. 2. Tuberculin, Am. J. Dis. Child. **83**: 598-602, May, 1952.

Tuberculosis 7371. Dickie, A. W.: Tuberculosis in families with BCG-vaccinated and non-vaccinated children, Brit. M. J. **1**: 682-686, Mar. 29, 1952.

7372. Symposium—streptomycin in bone and joint tuberculosis, J. Bone & Joint Surg. **34A**: 255-330, Apr., 1952.

7373. Peterson, J. C., et al.: Tuberculin hemagglutination studies in active tuberculous infections, benign and virulent, Acta paediat. **41**: 57-73, Jan., 1952.

7374. Vojtek, V., & Sery, Z.: Die extrapleurale Pneumolyse im Kindesalter, Schweiz. Ztschr. Tuberk. **9**: 141-146, No. 3, 1952.

Tuberculosis, BCG 7375. Wallgren, A.: BCG-vaccination as a public health measure, Edinburgh M. J. **59**: 161-177, Apr., 1952.

Tuberculosis, Ear Lobe 7376. Morgan, L. G.: Primary tuberculosis inoculation of an ear lobe, J. Pediat. **40**: 482-485, Apr., 1952.

Tuberculosis, Pulmonary 7377. Widmer, H. K.: Ueber die Prognose der offenen Lungentuberkulose bei Kindern und Jugendlichen, Schweiz. Ztschr. Tuberk. **9**: 147-167, No. 3, 1952.

7378. Blair, L. G.: The differential diagnoses in children of the pulmonary manifestations of primary tuberculosis and its immediate sequelae, Brit. J. Tuberc. **46**: 83-86, Apr., 1952.

7379. Allison, S. T.: Dihydrostreptomycin sulfate in pulmonary tuberculosis, Am. Rev. Tuberc. **65**: 612-616, May, 1952.

Tuberculosis, Tongue 7380. Jeannin, M.: A propos d'un cas de tuberculose primo-secondaire de la langue chez l'enfant, Pédiatrie **41**: 171-179, No. 2, 1952.

Tumors 7381. Fèvre, M.: Tumeurs malignes des os chez l'enfant, Ann. paediat. **178**: 477-479, Apr., 1952.

Tumors, Adrenal 7382. Cahill, G. F.: Pheochromocytoma: Diagnosis and treatment, Tr. West. S. A. **18**: 22-29, June, 1951.

Tumors, Bone 7383. Maylahn, D. J.: Thorn-induced "tumors" of bone, J. Bone & Joint Surg. **34A**: 386-388, No. 2, Apr., 1952.

Tumors, Intestine 7384. Cornet, P.: Epithélioma glandulaire cylindrique de type colloïde de l'intestin grêle, révélé, par une invagination iléo-iléale, chez un fillette de 4 ans, Pédiatrie **41**: 224-228, No. 2, 1952.
See No. 7243.

Tumors, Jaw 7385. Girwood, W.: Jaw tumors. 2. Benign tumours and cysts, South African M. J. **26**: 262-267, Mar. 29, 1952.

Tumors, Kidney 7386. Kaplan, J. H., et al.: Hypernephroma in an 8-year-old child, California Med. **76**: 297-8, Apr., 1952.

7387. Levant, B., & Feldman, B. J.: Traumatic rupture of Wilms' tumor, J. Urol. **67**: 629, May, 1952.

Tumors, Neck 7388. Barrington-Ward, Sir L.: Swellings of the neck in childhood, Ann. Roy. Coll. Surgeons England **10**: 211-227, Apr., 1952.

Tumors, Pancreas 7389. Warthen, R. O., et al.: Primary malignant tumor of the pancreas in a fifteen-month-old boy, Am. J. Dis. Child. **83**: 663-666, May, 1952.

Urecholine 7390. Jones, J. A., et al.: The gastric response of normal children to urecholine, J. Pediat. **40**: 456-461, Apr., 1952.

Urinary Tract. See No. 7326.

Varicella, Hemorrhagic 7391. Batch, J. W., & Sepkowitz, S.: Varicella complicated by gangrene of the lower extremities, U. S. Armed Forces J. **3**: 759-764, May, 1952.

Vitamins 7392. Merrow, S. B., et al.: Relationships between intake and serum levels of ascorbic acid, vitamin A and carotene of selected groups of children with physical signs of vitamin deficiencies, J. Nutrition **46**: 445-458, Apr. 10, 1952.

Wilson's Disease 7393. Uzman, L. L., & Hood, B.: The familial nature of the amino-aciduria of Wilson's disease (hepatolenticular degeneration), Am. J. M. Sc. **223**: 392-400, Apr., 1952.

Wissler-Fanconi Syndrome. See No. 7343.

Current Pediatric References

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Abscess, Brain 7394. Symposium—Clinicopathological conference, Clin. Proc. Child. Hosp., Wash., D. C. **8:** 125-131, May, 1952.

Accidents 7395. Rosenfield, A. B.: Childhood mortality from accidents, Minnesota Med. **35:** 424-429, May, 1952.

Acrodynia 7396. Houet, René: Report of two cases of acrodynia appearing after calomel therapy but without excretion of mercury in the urine and cured with B.A.L., Acta paediat. **41:** 158-161, March, 1952.

ACTH 7397. Soffer, L. J.: ACTH and cortisone: physiologic and clinical considerations, M. Clin. North America, May, 1952.

7398. Hudson, G., et al.: Effect of repeated injections of ACTH upon the bone marrow, Brit. M. J. **1:** 999-1002, May 10, 1952.

See Nos. 7400, 7402, 7443, 7465, 7582, 7607, 7640, 7641, 7649, 7651, and 7711.

Aerosols 7399. Prigal, S. J.: Studies with steam generated aerosols, Ann. Otol. Rhin. & Laryng. **61:** 206-240, March, 1952.

Albers-Schönberg Disease. See osteopetrosis.

Albright's Syndrome. See No. 7555.

Allergy 7400. Cooke, R. A.: The use of corticotrophin (ACTH) and cortisone in allergic states, M. Clin. North America, May, 1952.

7401. Symposium—Pediatric allergy, Pediatries **9:** 630-636, May, 1952.

Anemia, Hemolytic 7402. Clin. Case No. 688—Severe Anemia, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3015-3019, May, 1952.

Anemia, Mediterranean 7403. Mooney, F. S.: The diagnosis of carriers of Cooley's anaemia, J. Clin. Path. **5:** 154-160, May, 1952.

7404. Portier, A., et al.: Thalassemie et syndromes neuro-hémolytiques, Presse méd. **60:** 725-728, May 14, 1952.

Anomalies 7405. Büchner, F.: Zur Biologie und Pathologie der Entwicklung, Med. Klin. **47:** 605-611, May 2, 1952.

See No. 7655.

Anomalies, Brain 7406. Willi, H.: Neurologisches aus dem Gebiet der Neugeborenen-pathologie, Ann. paediat. **178:** 297-317, May/June, 1952.

Anomalies, Esophagus. See No. 7493.

Anomalies, Eye 7407. Jelliffe, D. B.: Congenital cataract and maternal smallpox, J. Trop. Med. **55:** 99-100, May, 1952.

Anomalies, G. I. Tract 7408. Lam, R. C.: Agenesis of anus and rectum, Journal-Lancet **72:** 238-239, May, 1952.

Anomalies, G. U. Tract 7409. Arlien-Søborg, U.: Supernumerary ureter with ectopic orifice, Acta radiol. **37:** 183-188, Mar.-Apr., 1952.

Anomalies, Hand 7410. Wilson, J. N.: Dystrophy of the fifth finger, J. Bone & Joint Surg. **34-B:** 236-239, May, 1952.

Anomalies, Kidney 7411. Boissonnat, P.: Ectopie rénale double avec symphyse médiane (rein en galette) chez une fillette de dix-sept mois, Arch. franç. pédiat. **9:** 294-299, No. 3, 1952.

Anomalies, Lip 7412. Abramson, P. D.: Bilateral congenital clefts of the lower lip, Surgery **31:** 761-764, May, 1952.

7413. Clément, R., et al.: Malformation dite fistule congénitale des lèvres, Arch. franç. pédiat. **9:** 283, No. 3, 1952.

Anomalies, Monster 7414. Perlmutter, B., et al.: Etude anatomo-radiologique d'un monstre double, Arch. franç. pédiat. **9:** 521-526, No. 5, 1952.

Anomalies, Ovarian 7415. Symposium—Malformational syndrome suggesting ovarian agenesis in preadolescence, J. Pediat. **40:** 651-661, May, 1952.

Anomalies, Visceral 7416. Winckler, G.: Multiples malformations viscérales chez un nouveau-né, Arch. Anat. Histol. & Embryol. **34:** 451-458, No. 1/8, 1951/52.

Anoxia 7417. Alajouanine, Th., et al.: Étude des lésions cérébrales de l'anoxie au cours des paralysies respiratoires, Rev. neurol. **86:** 3-24, No. 1, 1952.

See No. 7591.

Antibiotics 7418. McCurdy, R. S., & Neter, E.: Effects of penicillin and broad-spectrum antibiotics on the emergence of a gram-negative bacillary flora in the upper respiratory tract of infants, Pediatrics **9:** 572-576, May, 1952.

7419. Ahern, J. J., et al.: Lack of interference of chloramphenicol with penicillin in a hemolytic streptococcal infection in mice. (19449), Proc. Soc. Exper. Biol. & Med. **79:** 568-571, April, 1952.

7420. Dalgleish, P. G.: On reactions with the newer antibiotics, Bristol Med.-Chir. J. **69:** 54-56, April, 1952.

See Nos. 7435, 7705.

Appendicitis 7421. Snyder, W. H., Jr., & Chaffin, L.: Appendicitis during first two years of life, Arch. Surg. **64:** 549-560, May, 1952.

7422. Benson, C. D., et al.: Acute appendicitis in infants, Arch. Surg. **64:** 561-570, May, 1952.

See No. 7560.

Arteriovenous Fistula 7423. Symposium—Arteriovenous fistula in the neck, J. Pediat. **40:** 661-667, May, 1952.

Asthma 7424. Bullen, S. S., Sr.: Correlation of clinical and autopsy findings in 176 cases of asthma, J. Allergy **23:** 193-203, May, 1952.

7425. Rackemann, F. M., & Edwards, M. C.: Asthma in children. A follow-up study of 688 patients after an interval of twenty years, New England J. Med. **246:** 815-823, May 22, 1952.

Atelectasis 7426. Martin, J. F., & Friedell, H. L.: The roentgen findings in atelectasis of the newborn, Am. J. Roentgenol. **67:** 905-923, June, 1952.

7427. Jersild, T., & Riskaer, N.: L'atélectasie pulmonaire infectieuse aigue simulant une broncho-pneumonie chez le nourrisson, Arch. franç. pédiat. **9:** 254-265, No. 3, 1952.

Banthine. See No. 7444.

Bell's Palsy 7428. Bierman, Wm.: Diagnosis and treatment of Bell's palsy, J. A. M. A. **149:** 253-258, May 17, 1952.

Biliary Atresia 7429. Whitten, W. W., & Adie, G. C.: Congenital biliary atresia, J. Pediat. **40:** 539-548, May, 1952.

Bites, Insect 7430. Goldman, L.: Local effect of compound F on reactions to mosquito bites, J. A. M. A. **149:** 265, May 17, 1952.

Blood, Nuclear Anomaly 7431. Begemann, N. H., & Campagne, A. Van L.: Homozygous form of Pelger-Huët's nuclear anomaly in man, Acta haemat. **7:** 295-303, May, 1952.

Blood, Reticulocytes 7432. Klosenow, W.: Ein Beitrag zur Frage der sog. Achromoretikulocyten, Ztschr. Kinderh. **70:** 623-632, No. 6, 1952.

Bone, Pseudoepiphyses 7433. Weinert, P.: Ein Beitrag zur Frage der Pseudoepiphysen, Anatomischer Anzeiger **99:** 1-18, Mar. 15, 1952.

Breast Feeding 7434. Miller, R. A.: The assessment of inadequate lactation, Edinburgh M. J. **59:** 238-246, May, 1952.

Bronchitis 7435. Mulder, J., et al.: Studies on the treatment with antibacterial drugs of acute and chronic mucopurulent bronchitis caused by Hemophilus influenzae, Acta. med. scandinav. **143:** 32-49, No. 1, 1952.

Brucellosis 7436. Léon, A. P., et al.: Antibiotics and immunodesensitization in the treatment of human brucellosis, Science **115:** 576-577, May 23, 1952.

Burns 7437. McLaughlin, C. W., Jr., & Neis, D. K.: Recent advances in the management of burns, Am. J. Surg. **83:** 746-754, June, 1952.

Cancrum Oris. See No. 7501.

Celiac Disease 7438. Morgan, G. D., & Tylden, E.: Coeliac disease, Lancet **1:** 973-974, May 10, 1952.

Cerebral Palsy 7439. Hughes, J. G.: Early detection of cerebral injury, J. Pediat. **40:** 606-620, May, 1952.

Cerebrospinal Fluid 7440. Michaux, L., & Chauderlot, B.: Renseignements fournais par l'étude fractionnée du liquide céphalo-rachidien en neuro-psychiatrie infantile, Arch. franç. pédiat. **9:** 517-520, No. 5, 1952.

Chloromycetin 7441. Sandmann, F.: Das Verhalten des Darmes bei Chloromycetin-medikation, Deutsche med. Wchnschr. **77:** 557-558, April 25, 1952.

See No. 7569.

Cholecystitis 7442. Symposium—Chronic cholecystitis and cholelithiasis in a 2½-month-old infant, J. Pediat. **40:** 667-671, May, 1952.

Chondrodystrophy, Atypical. See No. 7464.

Chorea 7443. Heuyer, et al.: Premiers essais de traitement de la chorée de Sydenhan par l'ACTH, Arch franç pédiat. **9:** 303, No. 3, 1952.

Colic 7444. Levy, H., & Zweifler, B. M.: The use of Banthine bromide in infantile colic and vomiting, J. Pediat. **40:** 570-575, May, 1952.

Colitis, Ulcerative 7445. Sanford, M. C., et al.: Chronic ulcerative colitis, Clin. Proc. Child. Hosp., Wash., D. C. **8:** 106-117, May, 1952.

Constipation 7446. Vignec, A. J., & Mitty, V. C.: Treatment of constipation in infancy and childhood, J. Pediat. **40:** 576-578, May, 1952.

Convulsions 7447. Pascual, R., & McGovern, J. P.: Febrile convulsions in childhood, Clin. Proc. Child. Hosp., Wash., D. C. **8:** 92-98, May, 1952.

Cortisone. See Nos. 7397, 7400, 7465, 7466, 7583, 7607, 7648, and 7649.

Coxa Vara 7448. Johanning, K.: Coxa vara infantum. I. Clinical appearance and aetiological problems, Acta orthop. scandinav. **21:** 273-299, No. 4, 1951.

Coxsackie Viruses 7449. Top, F. H.: The Coxsackie viruses: with a consideration of their relationship to the virus of poliomyelitis, Ztschr. Hyg. **134:** 183-187, No. 2, 1952.
See No. 7535.

Croup. See No. 7554.

Cysts, Mediastinal 7450. Chaptal, J., et al.: Kyste congénital du médiastin postérieur chez un enfant de 5 ans intervention. Guérison, Arch. franç. pédiat. **9:** 313-316, No. 3, 1952.

Cysts, Ovarian 7451. Clin. Case No. 682—Movable mass in the abdomen, Case Rep. Child. Mem. Hosp., Chicago, Ill. **10:** 2093-2094, April, 1952.

Deafness 7452. Johnsen, S.: Natal causes of perceptive deafness, Acta oto-laryng. **42:** 51-63, Feb.-Apr., 1952.

Dermatomyositis 7453. Backmann, Carl-Heinz: Beitrag zum Krankheitsbild der Dermatomyositis, Monatschr. Kinderh. **100:** 79-83, March, 1952.

Diabetes 7454. Engel, R., et al.: Observations on two children with diabetes mellitus and epilepsy, Journal-Lancet **72:** 242-248, May, 1952.

7455. Dolger, H.: The management of insulin allergy and insulin resistance in diabetes mellitus, M. Clin. North America, May, 1952.

7456. Peters, J. P.: Diabetic acidosis, Metabolism **1:** 223-235, May, 1952.

7457. Brodribb, H. S., et al.: Two cases of diabetes mellitus in infants under 1 year, Brit. M. J. **1:** 1060-1061, May 17, 1952.

Diarrheal Diseases 7458. Darrow, D. C.: Therapeutic measures promoting recovery from the physiologic disturbances of infantile diarrhea, Pediatrics **9:** 519-533, May, 1952.

7459. Droese, W.: Zur Pathogenese und Therapie der Toxikose im Säuglingsalter, Arch. Kinderh. **144:** 98-124, No. 2, 1952.

7460. Forsander, O., & Hallman, N.: On free plasma choline in severe infantile gastro-enteritis, Scandinav. J. Clin. & Lab. Invest. **4:** 63-67, No. 1, 1952.

Diastematomyelia 7461. Cowie, T. N.: Diastematomyelia: tomography in diagnosis, Brit. J. Radiol. **25:** 263-266, May, 1952.

Diet 7462. Mouriquand, G.: Alimentation et régimes des enfants d'âge scolaire, J. méd. Lyon. No. 775: 395-407, Apr. 20, 1952.

Dyslexia 7463. Symposium—Un cas de Dyslexie spécifique, Semaine hôp. Paris **28:** 1455-1477, May 10, 1952.

Dysostosis Endochondralis 7464. Kniest, W.: Zur Abgrenzung der Dysostosis enchondralis von der Chondrodystrophie, Ztschr. Kinderh. **70:** 633-640, No. 6, 1952.

Eczema 7465. Glaser, J.: Treatment with ACTH and cortisone of atopic dermatitis (eczema) in infants and children, J. Allergy **23:** 222-228, May, 1952.

7466. Schreier, K.: Ueber die Behandlung des kindlichen Ekzems mit Cortison, Deutsche med. Wchnschr. **77:** 654-655, May 16, 1952.

7467. Nomland, R.: Symptomatic treatment of eczema and dermatitis, Postgrad. Med. **11:** 412-414, May, 1952.

Edema, Nutritional 7468. Chedid, P., et al.: L'exsiccose avec oedémes de la première enfance, Arch. franç. pédiat. **9:** 507-510, No. 5, 1952.

Electrocardiography 7469. Easby, M. H., et al.: Effect of viral infections on the heart as reflected in the electrocardiogram, J. Am. M. Women's A. **7:** 157-166, May, 1952.

7470. Schaffer, A. I., et al.: The effect of eccentricity on spatial vector analysis of the electrocardiogram of the newborn infant and on the correlation between the electrocardiogram and the vectorcardiogram, Am. Heart. J. **43:** 735-742, May, 1952.

Electroencephalography 7471. Symposium—Die Elektroencephalographie im Kindesalter, Monatschr. Kinderh. **100:** 200-224, April, 1952.
See No. 7511.

Electrolytes 7472. Berger, E. Y., & Steele, J. M.: Electrolyte and water metabolism: physiologic considerations, M. Clin. North America, May, 1952.

7473. Hill, F. S.: Respiratory acidosis and alkalosis, South. M. J. **45:** 521-525, June, 1952.

Emphysema, Congenital 7474. Razemon, P., & Breton, A.: Etude anatomo-radio-clinique d'un emphysème lobaire supérieur géant, chez un nourrisson de un mois, Arch. franç. pédiat. **9:** 286-290, No. 3, 1952.

Encephalitis, Herpetic. See No. 7688.

Encephalomyelitis, Hemorrhagic 7475. Giedion, A.: Die hämorrhagische Encephalomyelitis postvaccinalis, Schweiz. Ztschr. allg. Path. **15:** 234-253, No. 2, 1952.

Encephalopathy, Immunization 7476. Sher, D. A.: Encephalopathy following pertussis vaccine, Journal-Lancet **72:** 249-251/271, May, 1952.

Encopresis 7477. Biermann, H.: Enkopresis als psychogene Reaktion, Monatschr. Kinderh. **100:** 228-229, April, 1952.

Endocarditis, Bacterial 7478. Path. Case No. 680—Bacterial endocarditis, Case Rep. Child. Mem. Hosp., Chicago, Ill. **10:** 2087-2090, April, 1952.

Endocarditis, Staphylococcic 7479. Dowling, H. F., et al.: Staphylococcic endocarditis: an analysis of 25 cases treated with antibiotics, together with a review of the recent literature, Medicine **31:** 155-176, May, 1952.

Enuresis 7480. Brock, H.: Vergelich zwischen Psychotherapierten und unbehandelten kindlichen Bettnässern, Monatschr. Kinderh. **100:** 86-89, March, 1952.

Eosinophilic Granuloma 7481. Cathala, J., & Auzépy, P.: Granulome eosinophilique de l'os Nourrisson **40:** 1-14, No. 1, 1952.

7482. Kaplan, M., et al.: A propos d'une observation de granulome éosinophilique a forme diffuse chez un enfant de cinq ans. Rapports de cette affection avec les réticuloses voisines, Arch. franç. pédiat. **9:** 237-253, No. 3, 1952.

7483. Pliess, G.: Das Eosinophile granuloreticulom, Arch. path. Anat. **321:** 355-377, No. 4, 1952.

Eosinophils 7484. Jennings, P. P.: Adrenal cortical function at death as measured by level of circulating eosinophils, Brit. M. J. **1:** 1055-1058, May 17, 1952.

Epilepsy 7485. Thompson, R.: A consideration of some of the problems presented by epilepsy, Irish J. M. Sc. No. 317: 227-234, May, 1952.

7486. Jewesbury, E. C. O.: The electroencephalogram in doubtful cases of epilepsy, Lancet **1:** 1029-1031, May 24, 1952.

Epiphyseal Dysgenesis 7487. Paus, B.: Madelung's deformity; its etiology and pathogenesis, Acta orthop. scandinav. **21:** 249-258, No. 4, 1951.

7488. Mosekilde, E.: Stippled epiphyses in the newborn and in infants, Acta radiol. **37:** 291-307, Mar.-Apr., 1952.

Erythroblastosis Fetal 7489. Dunne, Chas. J., & Innella, F. P.: Dual sensitization to the Rh (E) and Hr (e) factors detected antenatally. A case report, Blood **7:** 526-532, May, 1952.

7490. Hirszfeld, H., et al.: Destinée des enfants provenant de grossesses conservées par les moyens antiallergiques, Schweiz. med. Wchnschr. **82:** 502-503, May 3, 1952.

7491. Johnsen, S., & Friesleben, E.: The relation between erythroblastosis foetalis, kernicterus and impairment of hearing, Acta oto-laryng. **42:** 35-50, Feb.-Apr., 1952.

7492. Seelemann, K.: Die Differentialdiagnose der Erythroblastosis foetalis, Ztschr. Kinderh. **71:** 61-78, No. 1, 1952.

Esophagus, Anomaly 7493. Roviralta, E.: Sur l'origine du brachyoesophage, Arch. franç. pédiat. **9:** 280-282, No. 3, 1952.

Esophageal Dystonia 7494. Cross, F. S.: Pathologic changes in megaesophagus (esophageal dystonia), Surgery **31:** 647-653, May, 1952.

Estrogenic Hormones. See No. 7660.

Facial Asymmetry 7495. Boder, E.: Facial asymmetry in the newborn infant: its relation to congenital cranial osteoporosis (craniotabes) and infant's birth order, J. Pediat. **40:** 558-564, May, 1952.

Feeding 7496. Chalmers, J. A.: The vitamin B complex as a supplement in infant feeding, Edinburgh M. J. **59:** 247-254, May, 1952.

Fluids. See No. 7458 and 7472.

Foreign Body, Esophagus 7497. Tompsett, A. C., Jr.: Respiratory symptoms due to esophageal foreign bodies in infants, Wisconsin M. J. **51:** 481-482, May, 1952.

Foreign Body, G. I. Tract 7498. Dorenbusch, A. A.: Ferromagnetic foreign bodies beyond the pylorus, Arch. Otolaryng. **55:** 589-596, May, 1952.

Foreign Body, Nose 7499. Wilson, K. L.: Foreign body in adenoids, J. Laryng. & Otol. **66:** 243, May, 1952.

Gangrene, Extremities 7500. Askue, W. E., & Wong, R.: Gangrene of the extremities in the newborn infant, J. Pediat. **40:** 588-598, May, 1952.

Gangrene, Mouth 7501. Jelliffe, D. B.: Infective gangrene of the mouth, Pediatrics **9:** 544-550, May, 1952.

Gargoylism 7502. Brante, G.: Gargoylism—a mucopolysaccharidosis, Scandinav. J. Clin. & Lab. Invest. **4:** 43-46, No. 1, 1952.

7503. Andersson, B., & Tandberg, O.: Lipochondystrophy (gargoylism, Hurler's syndrome) with specific cutaneous deposits, Acta pediat. **41:** 162-167, March, 1952.

Glaucoma 7504. Robertson, E. N., Jr.: Surgical treatment of congenital glaucoma, Arch. Ophth. **47:** 611-615, May, 1952.

7505. Thomas, Ch., & Algan, B.: La cyclodie thermie perforante intervention de choix dans le traitement du glaucome infantile, Ann. ocul. **185:** 155-169, Feb., 1952.

Goiter 7506. Bauer, J.: Der kindliche Kropf und seine Verhütung, Med. Klin. **47:** 530-535, Apr. 18, 1952.

Growth 7507. Wilde, E.: The treatment of growth failure in Aleut school children, J. Pediat. **40:** 565-569, May, 1952.

7508. Freund, J., & Maier, E. H.: Zur Aetiologie der Entwicklungsbeschleunigung, Ztschr. Kinderh. **71:** 1-33, No. 1, 1952.

Hallervorden-Spatz Syndrome 7509. De Jong, R. N.: Clinical pathologic study of Hallervorden-Spatz syndrome, Arch. Neurol. & Psychiat. **67:** 685-686, May, 1952.

Hearing 7510. Sataloff, J.: Acoustic trauma in children, Ann. Otol. Rhin. & Laryng. **61:** 106-111, March, 1952.

7511. Gidoll, S. H.: Quantitative determination of hearing to audiometric frequencies in the electroencephalogram, Arch. Otolaryng. **55:** 597-601, May, 1952.

7512. Bangs, J. L., and Bangs, T. E.: Hearing aids for young children, Arch. Otolaryng. **55:** 528-535, May, 1952.

7513. Watson, T. J.: Ascertainment of the needs for special educational treatment in children of school age with defective hearing, Acta oto-laryng. **40:** 361-369, No. 5-6, 1951-1952.

7514. Hardy, Wm. G., & Bordley, J. E.: Evaluation of hearing in young children, Acta oto-laryng. **40:** 346-360, No. 5-6, 1951-1952.

Heart, Angiocardiography 7515. Lind, J., & Wegelius, C.: Angiocardiographic studies in children, Advances in Pediatrics **5:** 154-194, Year Book Publishers, 1952.

Heart, Coronary Arteriosclerosis 7516. Sladden, R. A.: Coronary arteriosclerosis and calcification in infancy, J. Clin. Path. **5:** 175-182, May, 1952.

Heart, Dynamics 7517. Kirchhoff, H., & Jacobi, G. W.: Kreislaufgrössen und Kreislaufregulation im Kindesalter, Ztschr. Kinderh. **70:** 578-587, No. 6, 1952.

7518. Jacobi, G. W., & Kirchhoff, H.: Die Anspannungs und Austreibungszeit als funktionsprüfung des kindlichen Herzens, Ztschr. Kinderh. **70:** 561- 567, No. 6, 1952.

7519. Hockerts, Th.: Untersuchungen über den Einfluss vegetativer Erregung auf die Dynamik des kindlichen Herzens, Ztschr. Kinderh. **70:** 535-540, No. 6, 1952.

Heart Disease, Congenital 7520. Symposium—Die angeborenen Herzfehler, Monatschr. Kinderh. **100:** 107-149, Apr., 1952.

7521. Anderson, R. M., & McKee, E. E.: Congenital tricuspid atresia, Am. Heart J. **43:** 761-764, May, 1952.

7522. McAleese, J. J.: A survey of congenital heart disease in a children's hospital, Am. J. Surg. **83:** 755-760, June, 1952.

7523. Ash, R.: Position of aortic arch and descending aorta, Am. J. Roentgenol. **67:** 924-928, June, 1952.

7524. Nadas, A. S., & Alimurung, M. M.: Apical diastolic murmurs in congenital heart disease, Am. Heart J. **43:** 691-706, May, 1952.

7525. Soulié, P., et al.: Contribution a l'étude des malformations cardiaques congénitales associées aux dextrocardies, Semaine hôp. Paris **28:** 1334-1344, Apr. 30, 1952.

7526. Potts, W. J.: The tetralogy of Fallot, Am. J. Med. **12:** 596-602, May, 1952.

7527. Bertove, P., et al.: Cardiopathie congénitale chez des jumeaux dizygotes par embroypathie, J. méd. Lyon No. 775: 391-393, Apr. 20, 1952.

Heart Disease, Traumatic 7528. Vesterdal, J.: Traumatic heart disease in a 6-year-old girl, Acta paediat. **41:** 185-191, March, 1952.

Hemangioma, Buttocks 7529. Clin. Case No. 684: Cerebriform nevus, Clin. Rep. Child. Mem. Hosp., Chicago, Ill. **10:** 2097-2099, April, 1952.

Hemorrhagic Diseases 7530. Dam, H., et al.: The relation of vitamin K deficiency to hemorrhagic disease of the newborn, Advances in Pediatrics **5:** 129-153, Year Book Publishers, 1952.

7531. De Sousa, C. S.: A propos de la tendance hémorragique du nouveau-né, Arch. franç. pédiat. **9:** 482-491, No. 5, 1952.

Hepatitis 7532. Path. Case No. 685: Distended abdomen, Clin. Rep. Child. Mem. Hosp. Chicago, Ill. **10:** 3000-3003, April, 1952.

7533. Denber, H. C. B., & Leibowitz, S.: Acute anicteric virus hepatitis, J. A. M. A. **149:** 546-549, June 7, 1952.

Hernia, Diaphragmatic 7534. Clin. Case No. 689—Mass in chest, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3020-3022, May, 1952.

Herpangina 7535. Parrott, R. H., et al.: Further observations on herpangina and its relation to the Coxsackie group of viruses, Clin. Proc. Child. Hosp., Wash., D. C. **8:** 118-124, May, 1952.

Hydrocephalus 7536. Epstein, B. S.: Separation of the blood vessels from the walls of a lateral ventricle in rapidly progressing hydrocephalus, Am. J. Roentgenol. **67:** 929-931, June, 1952.

Hypertension 7537. Seelemann, K., & Linnekogel, G.: Ueber den Hochdruck im Kindesalter bei einseitiger Nierenerkrankung, Ztschr. Kinderh. **70:** 568-577, No. 6, 1952.

Hypoglycemia 7538. Greenlee, R. G., et al.: Chronic hypoglycemia in an infant treated by subtotal pancreatectomy, J. A. M. A. **149:** 272, May 17, 1952. See No. 7609.

Immunization 7539. Benenson, A. S., et al.: Problems in maintaining immunity to smallpox, Am. J. Pub. Health **42:** 535-541, May, 1952.

Incontinentia Pigmenti 7540. Epstein, S., et al.: Bullous variety of incontinentia pigmenti (Bloch-Sulzberger), Arch. Dermat. & Syph. **65:** 557-567, May, 1952.

7541. Franklin, A. W.: Incontinentia pigmenti (Bloch-Sulzberger), Proc. Roy. Soc. Med. **45:** 219, April, 1952.

Infection Nosocomial 7542. Laurell, G.: Airborne infections. 6. Continued investigations into the control of dust-borne streptococcal infections in infants' wards, Acta paediat. **41:** 124-137, March, 1952.

Influenza 7543. Smith, W.: The structural and functional plasticity of influenza virus, Lancet **1:** 885-891, May 3, 1952. See No. 7435.

Infusion, Technique 7544. Barrie, H.: An infusion splint for infants, Lancet **1:** 1001, May 17, 1952.

Intestine, Obstruction 7545. Rack, F. J., & Crouch, W. L.: Functional intestinal obstruction in the premature newborn infant, J. Pediat. **40:** 579-583, May, 1952.

7546. McLaughlin, C. W., Jr., & Coe, J. D.: Acute intestinal obstruction in infancy, Arch. Surg. **64:** 541-548, May, 1952.

7547. Gérard-Lefebvre & Bonte, G.: Volvulus gastrique chez un nourrisson de 11 mois porteur de malformations congénitales multiples, Arch. franç. pédiat. **9:** 546-550, No. 5, 1952.

Intussusception 7548. Hesser, H. H., et al.: Gangrenous intussusception, J. Kansas M. Soc. **53:** 217-219, May, 1952.

7549. Nordentoft, J. M.: The reduction of intussusception in children by barium enemata, Acta radiol. **37:** 341-347, Mar.-Apr., 1952. See No. 7546.

Iron, Metabolism 7550. Smith, C. H., et al.: Iron metabolism in infants and children. Serum iron and iron-binding protein—diagnostic and therapeutic implications, Advances in Pediatrics **5:** 195-231, Year Book Publishers, 1952.

7551. Feuillen, Y. M., & Plumier, M.: Iron metabolism in infants. 1. The intake of iron in breast feeding and artificial feeding (milk and milk foods), Acta paediat. **41:** 138-144, March, 1952.

Kidney, Polycystic 7552. Adlerman, E. J.: Familial incidence in polycystic kidney disease, Am. J. Surg. **83:** 787-793, June, 1952.

Kwashiorkor. See No. 7558.

Lactobacillus Bifidus 7553. Braun, O. H., & Marget, W.: Beitrag zur Züchtung und Differenzierung von Lactobacillus bifidus, Ztschr. Kinderh. **70:** 641-648, No. 6, 1952.

Laryngotracheitis 7554. Gilbert, J. G., et al.: Infectious nondiphtheritic croup, Arch. Otolaryng. **55:** 566-581, May, 1952.

Leontiasis Ossea 7555. Millichap, J. G.: Leontiasis ossea, skeletal precocity—possible Albright's syndrome, Proc. Roy. Soc. Med. **45:** 217-218, April, 1952.

Lithiasis, Urinary 7556. Weill, J., & Boissonnat, P.: Lithiase urinaire multiple de l'enfant, Arch. franç. pédiat. **9:** 291-294, No. 3, 1952.

Lung, Volume 7557. Morse, M., et al.: The lung volume and its subdivisions in normal boys 10-17 years of age, J. Clin. Investigation **31:** 380-391, April, 1952.

Madelung's Deformity. See Epiphyseal Dysgenesis.

Malnutrition 7558. Thompson, M. D., & Trowell, H. C.: Pancreatic enzyme activity in duodenal contents of children with a type of Kwashiorkor, Lancet **1:** 1031-1035, May 24, 1952.

Masturbation 7559. Bakwin, H.: Masturbation in infants, J. Pediat. **40:** 675-678, May, 1952.

Measles 7560. Bonenfant, J. L.: Lésions appendiculaires au cours de la rougeole, Arch. franç. pédiat. **9:** 497-506, No. 5, 1952.

Mediastinum, Tomography 7561. Sansone, G., & De Maestri, A.: The simultaneous visualization of the posterior and anterior mediastinum after insufflation in the peridural space. Tridimensional tomographic study, Acta paediat. **41:** 101-107, March, 1952.

Megacolon 7562. State, D.: Physiological operation for idiopathic congenital megacolon (Hirschsprung's disease), J. A. M. A. **149:** 350-355, May 24, 1952.

Meningitis 7563. Motsay, D. S., & Fisher, W. A.: Meningitis: a ten-year pediatric survey, Guthrie Clin. Bull. **21:** 129-139, April, 1952.

Meningitis, Bacterial 7564. Jones, H. E.: Subdural effusions in purulent meningitis, Lancet **1:** 891-893, May 3, 1952.

7565. Alexander, H. E.: Advances in the treatment of bacterial meningitis, Advances in Pediatrics **5:** 13-52, Year Book Publishers, 1952.

Meningitis, Influenzal 7566. Editorial—Haemophilus meningitis, Lancet **1:** 1003-1004, May 17, 1952.

Meningitis, Pneumococcal 7567. Bunn, P. A., & Peabody, G.: Treatment of pneumococcal meningitis with large doses of penicillin, Arch. Int. Med. **89:** 736-742, May, 1952.

Meningitis, Purulent 7568. Anglin, C. S., et al.: Acute purulent meningitis in childhood, Canad. M. A. J. **66:** 435-439, May, 1952.

Meningitis, Salmonella 7569. Kantor, H. L.: Salmonella Bredeney meningitis, Pediatrics **9:** 597-601, May, 1952.

Meningitis, Tuberculous 7570. Bernheim, M., & Lanternier, J.: La phase latente de la méningite tuberculeuse chez l'enfant, J. méd. Lyon No. 775: 383-389, Apr. 20, 1952.

7571. Giraud, P., & Espinas, J.: La streptokinase dans les méningites tuberculeuses, Semaine hôp. Paris **28:** 1302-1304, Apr. 26, 1952.

Meningoencephalitis 7572. Symposium—Die sogen. abakteriellen Encephalomeningitiden, Monatschr. Kinderh. **100:** 154-186, April, 1952.

Methemoglobinemia, Congenital 7573. Gasul, B. M., et al.: Congenital Methemoglobinemia simulating tricuspid atresia, J. A. M. A. **149:** 258-260, May 17, 1952.

Mineral Metabolism 7574. McCrory, W. W., et al.: Renal excretion of inorganic phosphate in newborn infants, J. Clin. Investigation **31:** 357-366, April, 1952.

Molluscum Contagiosum 7575. Mopper, C.: Terramycin therapy of molluscum contagiosum, Arch. Dermat. & Syph. **65:** 613-614, May, 1952.

Mongolism. See No. 7633.

Mononucleosis, Infectious 7576. Thélin, F.: Rapports de la mononucléose infectieuse avec la diphtérie et les pneumonies atypiques, Rev. méd. Suisse Rom. **72:** 240-246, April, 1952.

Mortality, Fetal 7577. Steer, C. M., & Kosar, W. P.: The causes of fetal mortality at the Sloan Hospital for Women, 1940 to 1949, Am. J. Obst. & Gynec. **63:** 1091-1101, May, 1952.

7578. Diddle, A. W., et al.: Analysis of fetal mortality in cesarean section. Experience in an urban community, Am. J. Obst. & Gynec. **63:** 967-977, May, 1952.

Mortality, Infant 7579. Hofmeister, F. J., & Paegel, H.: Infant mortality in a voluntary hospital, Am. J. Obst. & Gynec. **63:** 999-1008, May, 1952.
See No. 7590.

Myocarditis 7580. Tudor, R. B., & Kling, R. R.: Isolated myocarditis in children, Journal-Lancet **72:** 235-237, May, 1952.

Nephritis 7581. Herbert, H. J.: Acute glomerulonephritis in childhood, J. Pediat. **40:** 549-557, May, 1952.
See No. 7683.

Nephrosis 7582. Kramer, B., et al.: Effect of the adrenocorticotropic hormone (ACTH) of nephrosis in childhood, Postgrad. Med. **11:** 439-446, May, 1952.

7583. Keith, N. M., et al.: Some effects of cortisone on metabolic disturbances associated with renal edema, Arch. Int. Med. **89:** 689-707, May, 1952.

7584. Barnett, H. L., et al.: The nephrotic syndrome in children, Advances in Pediatrics **5:** 53-128, Year Book Publishers, 1952.

7585. Symposium—Case report from the University of Kansas Medical Center, J. Kansas M. Soc. **53:** 240-246, May, 1952.

7586. Kropp, K., & Althoff, H.: Serumeiweissveränderungen bei Nephrosen und ihre Bedeutung für Therapie und Pathogenese, Ztschr. Kinderh. **70:** 588-612, No. 6, 1952.

Neurofibromatosis 7587. Franklin, A. W.: Von Recklinghausen's disease—neurofibromatosis with bone involvement, scoliosis and wedge-shaped deformity of thoracic vertebrae, Proc. Roy. Soc. Med. **45:** 218, April, 1952.
See No. 7631.

Newborn 7588. Craig, W. S.: Care of the neonate: instruction of the medical undergraduate, Brit. M. J. **1:** 1062-1063, May 17, 1952.

7589. Siddall, R. S., et al.: Effect on cesarean section babies of stripping or milking of the umbilical cords, Am. J. Obst. & Gynec. **63:** 1059-1064, May, 1952.

7590. Duncan, E. H. L., et al.: The causes and prevention of stillbirths and first week deaths. 1. The evidence of vital statistics, J. Obst. & Gynaec. Brit. Emp. **59:** 183-196, April, 1952.

7591. MacGregor, A. R.: The pathology of foetal and neonatal asphyxia, Edinburgh M. J. **59:** 229-238, May, 1952.

7592. Dochain, J., et al.: Principales donneés hématologiques chez le nouveauné normal, Arch. franç. pédiat. **9:** 274-278, No. 3, 1952.

7593. Wallace, H. M., et al.: Criteria for the evaluation of the quality of maternity and new-born care, Am. J. Pub. Health **42**: 499-507, May, 1952.

Nursing 7594. Shepard, W. P., & Wheatley, G. M.: Visiting nurse service, J. A. M. A. **149**: 554-557, June 7, 1952.

Osteochondritis, Juvenilis 7595. Gardemin, H.: Chronische Osteomyelitis und Perthessche Erkrankung, Ztschr. Orthop. **82**: 87-102, No. 1, 1952.

Osteomyelitis 7596. Batson, B. E.: Treatment of acute hematogenous osteomyelitis in children, South. M. J. **45**: 562-569, June, 1952.

Osteomyelitis, Nose 7597. Lance, P., & Meunier: Deux cas de destruction de la cloison nasale d'origine infectieuse, associée à ostéomyelite des membres, Arch. franç. pédiat. **9**: 284-286, No. 3, 1952.

Osteopetrosis 7598. Gérard-Lefebvre, et al.: Essai de greffe osseuse suivie de splénectomie chez un nourrisson atteint de maladie d'Albers-Schönberg à forme maligne précoce, Arch. franç. pédiat. **9**: 538-545, No. 5, 1952.

Osteoporosis 7599. Stevenson, F. H.: The osteoporosis of immobilisation in recumbency, J. Bone & Joint Surg. **34-B**: 256-265, May, 1952.

Ovarian Agenesis. See No. 7415.

Pancreas, Fibrocystic Disease 7600. Tobler, W.: Zur Behandlung der cystischen Pankreasfibrose mit Bronchiektasie (Dysporie) mit Antibiotics, unter Berücksichtigung der resultate von Resistenzprüfungen, Ann. paediat. **178**: 283-287, May/June, 1952.

Panniculitis 7601. McNicholl, B.: Scleroedema and myositis (? Panniculitis), Proc. Roy. Soc. Med. **45**: 220-221, April, 1952.

7602. Franklin, A. W.: Relapsing febrile nodular non-suppurative panniculitis (Weber-Christian Disease), Proc. Roy. Soc. Med. **45**: 219-220, April, 1952.

Para-aminosalicylic Acid 7603. Carr, D. T., et al.: Concentration of PAS and tuberculostatic potency of serum after administration of PAS with and without benemid, Proc. Staff Meet., Mayo Clin. **27**: 209-215, May 21, 1952.

Parathyroid Hyperplasia. See No. 7675.

Parathyroid, Hypofunction 7604. Path. Case No. 687—Idiopathic hypoparathyroidism, Case Reports Child. Mem. Hosp., Chicago, Ill. **10**: 3011-3015, May, 1952.

7605. Steinberg, H., & Waldron, B. R.: Idiopathic hypoparathyroidism: An analysis of fifty-two cases, including the report of a new case, Medicine **31**: 133-154, May, 1952.

Pelger-Huet's Anomaly. See Blood, Nuclear Anomaly.

Penicillin. See Nos. 7479, 7567 and 7682.

Pericarditis 7606. Friedman, S., et al.: Acute benign pericarditis in childhood: comparisons with rheumatic pericarditis, and therapeutic effects of ACTH and cortisone, Pediatrics **9**: 551-564, May, 1952.

Peritonitis, Tuberculous 7607. Kahrs, T.: Tuberculous peritonitis. A follow-up study of 169 cases, Tubercle **33**: 132-142, May, 1952.

Pertussis 7608. Henrich, H.: Cortineurin bei Pertussis, Med. Klin. **47**: 593, Apr. 25, 1952.

Pneumoencephalography 7609. Brandt, S., et al.: Misleading results of pneumoencephalography in an infant with severe hypoglycemic attacks, Acta paediat. **41**: 167-177, March, 1952.

Pneumonia, Atypical 7610. Chaptal, J., et al.: Formes cliniques de la grippe chez l'enfant au cours de l'hiver 1950-51, dans la région montpelliéraine, Arch. franç. pédiat. **9**: 449-481, No. 5, 1952. See No. 7576.

Pneumonia, Interstitial 7611. Vaněk, J., & Jirovec, O.: Parasitäre Pneumonie. Interstitielle Plasmazellen-pneumonia der frühgeborenen, verursacht durch Pneumocystis carinii, Zentralbl. Bakt. **158**: 120-127, May 12, 1952.

Poliomyelitis 7612. Path. Case No. 686—Poliomyelitis simulating tetanus, Case Reports Child. Mem. Hosp., Chicago, Ill. **10**: 3007-3011, May, 1952.

7613. Bower, A. G., et al.: Nitrogen and potassium metabolism: The reaction pattern in poliomyelitis, Am. J. M. Sc. **223**: 532-547, May, 1952.

7614. Bappert, W.: Psychosyndrome bei poliomyelitis, Ztschr. Kinderh. **70**: 613-622, No. 6, 1952.

Polyneuritis 7615. Clin. Case No. 681—Muscular weakness, Case Rep. Child. Mem. Hosp., Chicago, Ill. **10**: 2091-2092, Apr., 1952.

Prematurity 7616. Howard, P. J., & Worrell, C. H.: Premature Infants in later life. Study of intelligence and personality of 22 premature infants at ages 8-19 yrs., Pediatrics **9**: 577-584, May, 1952.

7617. Souchon, F., & Grunau, G.: Zur Amniosäurenausscheidung bei Frühgeborenen, Arch. Kinderh. **144**: 143-152, No. 2, 1952.

7618. Ducat, N.: L'avenir immediat des prematures nes et soignes dans une maternite, Nourrisson **40:** 18-22, No. 1, 1952.

7619. Bloch, H., et al.: Reduction of mortality in the premature nursery. I. The declining role of infection as a major cause of mortality in the modern premature nursery, J. Pediat. **40:** 584-587, May, 1952.

Prostatitis 7620. Alison, F., & Tan Vinh, L.: Prostatite aigue suppuree chez un nouveau-ne, Nourrisson **40:** 15-17, No. 1, 1952.

Pseudo-arthrosis 7621. Morris, D., & Hindenach, J. C. R.: Congenital pseudo-arthrosis in a newborn infant, Proc. Roy. Soc. Med. **45:** 224, April, 1952.

Pseudo-arthrosis, Leg 7622. Exner, G.: Zur Klinik und Pathogenese der angeborenen Verbiegungen und Pseudarthrosen des Unterschenkels, Ztschr. Orthop. **82:** 50-87, No. 1, 1952.

Psychiatry 7623. Barnes, M. J.: The educational and therapeutic implications in working with parent study groups around the problems of the normal preschool child, Am. J. Orthopsychiat. **22:** 268-276, April, 1952.

7624. Scheidlinger, S.: Group factors in promoting school children's mental health, Am. J. Orthopsychiat. **22:** 394-404, April, 1952.

7625. Krug, O., et al.: Intensive residential treatment of a nine-year-old girl with an aggressive behavior disorder, Petit mal epilepsy and enuresis, Am. J. Orthopsychiat. **22:** 405-427, April, 1952.

7626. Aberle, D. F., & Naegele, K. D.: Middle-class fathers' occupational role and attitudes toward children, Am. J. Orthopsychiat. **22:** 366-378, April, 1952.

7627. Nowlis, V.: The search for significant concepts in a study of parent-child relationships, Am. J. Orthopsychiat. **22:** 286-299, April, 1952.

7628. Lasko, J. K.: Parent-child relationships: report from the Fels Research Institute, Am. J. Orthopsychiat. **22:** 300-304, April, 1952.

7629. Cass, L. K.: An investigation of parent-child relationships in terms of awareness, identification, projection and control, Am. J. Orthopsychiat. **22:** 305-313, April, 1952.

Psychopathic Behavior 7630. Symposium—A differential study of psychopathic behavior in infants and children, Am. J. Orthopsychiat. **22:** 223, April, 1952.

Puberty, Precocious 7631. Piotti, A.: Pubertas praecox bei tumor der regio hypothalamica und neurofibromatose recklinghausen, Acta endocrinol. **10:** 66-88, No. 1, 1952.

7632. De Biehler, M.: Deux cas de puberté précoce chez des mongoliennes, Arch. franç. pédiat. **9:** 270-273, No. 3, 1952.

Pulmonary Edema 7633. Chaptal, J., et al.: L'oedème pulmonaire chez le nourrisson. Quarante-huit observations, Arch. franç. pédiat. **9:** 325-332, No. 3, 1952.

Pyelonephritis. See No. 7537.

Pylorospasm 7634. Harms, I.: Elektrokardiographische, kardiophonographische und blutchemische Untersuchungen bei Pylorospasmus. Die Bedeutung der Serumelektrolyte für die EKG-veränderungen bei Pylorospasmus, Arch. Kinderh. **144:** 125-143, No. 2, 1952.

7635. Jordan, G.: Beitrag zur Prophylaxe, Pathogenese und Therapie des Pylorospasmus, Ztschr. Hyg. **134:** 129-135, No. 2, 1952.

Radiology, Retroperitoneal 7636. Sansone, G.: La insufflazione retroperitoneale come mezzo di indagine radiologica nel bambino, Minerva med. **1:** 705-713, Apr. 5, 1952.

Respiratory Infections. See No. 7610.

Retrolental Fibroplasia 7637. Hepner, W. R.: Retrolental fibroplasia: animal studies. Induced vascular engorgement and hyperplasia of the iris, tunica vasculosa lentis and retina in kittens, Pediatrics **9:** 602-606, May, 1952.

7638. Hansen, E. W.: Retrolental fibroplasia, Postgrad. Med. **11:** 387-391, May, 1952.

7639. Reese, A. B., et al.: Results of use of corticotropin (ACTH) in treatment of retrolental fibroplasia, Arch. Ophth. **47:** 551-555, May, 1952.

7640. La Motte, W. O., Jr., et al.: Treatment of retrolental fibroplasia with vitamin E, corticotropin (ACTH) and cortisone, Arch. Ophth. **47:** 556-569, May, 1952.

7641. Bousquet, F. P., & Laupus, W. E.: Studies on the pathogenesis of retrolental fibroplasia, Am. J. Ophth. **35:** 64-68, May, 1952.

Retroperitoneal Insufflation. See No. 7636.

Rheumatic Disease 7642. Quinn, R. W., & Kincaid, C. K.: Rheumatic (valvular) heart disease in Madison, Wis. A survey of 7th grade school children, Am. J. M. Sc. **223:** 487-494, May, 1952.

7643. Taran, L. M., & Szilagyi, N.: Technical considerations in the measurement of the electrical systole (QT interval) and its relationship to the electrical events in the cardiac cycle. 2. The effect of cardiac rate upon the duration of the electrical systole, Bull. St. Francis Sanat., Roslyn, N. Y. **9:** 15-39, April, 1952.

7644. Gulotta, G. A.: Auricular fibrillation, Bull. St. Francis Sanat., Roslyn, N. Y. **9:** 39-43, April, 1952.

7645. Greene, M. H.: Protracted carditis of many years' duration resistant to treatment, Bull. St. Francis Sanat., Roslyn, N. Y. **9:** 43-47, April, 1952.

7646. Harris, T. N., & Friedman, S.: Phonocardiographic differentiation of vibratory (functional) murmurs from those of valvular insufficiency: further observations and application to the diagnosis of rheumatic heart disease, Am. Heart J. **43:** 707-712, May, 1952.

7647. Boone, J. A., & Beach, M. W.: Cortisone in acute rheumatic carditis, South. M. J. **45:** 556-558, June, 1952.

7648. McEwen, C.: The treatment of rheumatic fever with cortisone and ACTH, Bull. St. Francis Sanat., Roslyn, N. Y. **9:** 1-14, April, 1952.

Rheumatoid Arthritis 7649. Frus-Hansen, B., et al.: The effect of ACTH on body water compartment in juvenile rheumatoid arthritis, Scandinav. J. Clin. & Lab. Invest. **4:** 36-42, No. 1, 1952.

7650. Vesterdal, J., et al.: ACTH in the treatment of juvenile rheumatoid arthritis, Acta paediat. **41:** 145-157, March, 1952.

Rickets 7651. Lüttgens, P.-K.: Das Marfan-symptom bei der Rachitis, Ztschr. Kinderh. **70:** 541-551, No. 6, 1952.

Rubella 7652. Watson, J. R. H.: Hepatosplenomegaly as a complication of maternal rubella: a report of two cases, M. J. Australia **1:** 516-517, April 12, 1952.

7653. Günther, F. E.: Beitrag zur Pathogenese der Röteln-embryopathie, Arch. Kinderh. **144:** 152-185, No. 2, 1952.

7654. Müller, H. K.: Ueber die Embryopathia rubeolosa, Med. Klin. **47:** 611-614, May 2, 1952.

Salmonella Infection 7655. Villemin-Clog, L., et al.: Une épidémie d'infections a salmonella brandenburg dans une crèche de maternité, Arch. franç. pédiat. **9:** 225-236, No. 3, 1952.

Scarlet Fever 7656. Grün, L., et al.: Zur Scharlachätiologie, Ztschr. Kinderh. **71:** 34-41, No. 1, 1952.

Schizophrenia 7657. Bender, L., & Keeler, W. R.: The body image of schizophrenic children following electroshock therapy, Am. J. Orthopsychiat. **22:** 335-355, April, 1952.

Schüller-Christian Disease 7658. Sacrez, R., et al.: Maladie de Schüller-Christian du nourrisson, Arch. franç. pédiat. **9:** 511-515, No. 5, 1952.

Scurvy 7659. Hickley, J. M., & Stewart, B. B.: The history of scurvy, South African M. J. **26:** 293-297, Apr. 5, 1952.

Sexual Precocity 7660. Hesselvik, L.: Signs of sexual precocity in a male infant due to estrogenic ointment, Acta paediat. **41:** 177-185, March, 1952.

Splenic Puncture 7661. Chatterjea, J. B., et al.: Splenic puncture, Brit. M. J. **1:** 987-990, May 10, 1952.

Strabismus 7662. Stillerman, M. L., et al.: Electroencephalographic changes in strabismus, Am. J. Ophth. **35:** 54-63, May, 1952.

Streptokinase 7663. Metras, H., et al.: La streptokinase en pneumologie, Semaine hôp. Paris **28:** 1294-1302, Apr. 26, 1952. See No. 7571.

Subdural Abscess. See No. 7564.

Subdural Hematoma 7664. Marquézy, R. A., et al.: Hématome sous-dural et fractures multiples des os longs chez un nourrisson de 9 mois, Arch. franç. pédiat. **9:** 526-531, No. 5, 1952.

Syphilis 7665. Seyss, R., & Wiesner, E.: Das epiphysenwachstum bei lues congenita, Wien. med. Wchnschr. **102:** 306-307, Apr. 19, 1952.

Tapeworm, Dwarf 7666. Beaver, P. C., & Sodeman, W. A.: Treatment of Hymenolepis nana (dwarf tapeworm) infection with quinacrine hydrochloride (atebrin), J. Trop. Med. **55:** 97-99, May, 1952.

Teaching 7667. Symposium—The academy looks at pediatric education, Pediatrics **9:** 617-629, May, 1952.

Teeth 7668. Mackenzie, E. F. W.: The prevention of dental caries by the administration of fluorine in public water-supplies, Lancet **1:** 961-969, May 10, 1952.

7669. Knutson, J. W.: The case for water fluoridation, New England J. Med. **246:** 737-743, May 8, 1952.

Terramycin 7670. Hunt, A. D., Jr., et al.: Studies on absorption and distribution of terramycin in children, Pediatrics **9:** 607-616, May, 1952.

7671. Garrahan, J. P., et al.: Investigaciones sobre la concentración sanguinea de terramicina, en niños, Semana méd. **100:** 543-544, May, 1952.

7672. Garrahan, J. P., et al.: Terramycina en pediatria, Semana, méd. **100:** 545-546, May, 1952.

See No. 7575.

Tetanus 7673. Melnick, T.: Tetanus: A case without obvious portal of entry that recovered, Pennsylvania M. J. **55:** 443-445, May, 1952.

Tetany 7674. Kramer, B., & Leibner, I. W.: Tetany: Biochemical and clinical considerations, M. Clin. North America, May, 1952.

7675. Gardner, L. I.: Tetany and parathyroid hyperplasia in the newborn infant: Influence of dietary phosphate load, Pediatrics **9:** 534-543, May, 1952.

Thrombosis, Intracranial 7676. Chigneli, R.: Three cases of intracranial venous thrombosis following frontal sinusitis, J. Laryng. & Otol. **66:** 237-242, May, 1952.

Thyroid 7677. Reilly, W. A.: Thyroid problems in childhood, GP **5:** 43-46, June, 1952.

7678. Tänkä, H.: The weight of the thyroid gland in children of 0-2 years of age, Acta paediat. **41:** 108-123, March, 1952.

Thyroid, Hyperfunction 7679. Piper, D. W.: A case of childhood thyrotoxicosis, M. J. Australia **1:** 515-516, April 12, 1952.

Thyroid, Hypofunction 7680. Wilkins, L.: Hypothyroidism in childhood, Mississippi Doctor **30:** 1-3, June, 1952.

Tinea Capitis 7681. Schwebel, S., et al.: Ineffectiveness and toxicity of podophyllin in treatment of tinea capitis, J. A. M. A. **149:** 261, May 17, 1952.

Tonsils 7682. Lund, E., & Everberg, T.: Preoperative penicillin therapy in tonsillectomy, Acta oto-laryng. **42:** 125-130, Feb./Apr., 1952.

7683. Lumio, J. S.: Effect of acute tonsillitis and tonsillectomy on the course of nephritis, Acta oto-laryng. **42:** 113-125, Feb./Apr., 1952.

7684. Dey, D. L.: A survey of 681 children awaiting tonsillectomy and the indications for operation in childhood, M. J. Australia **1:** 510-514, April 12, 1952.

Toxicosis. See No. 7459.

Toxoplasmosis 7685. Keller, W., & Vivell, O.: Ueber die klinische und epidemiologische Bedeutung des Antikörpernachweises gegen das Toxoplasma gondii mit dem Sabin-Feldmanschen Farbtest, Ztschr. Kinderh. **71:** 42-60, No. 1, 1952.

7686. Paul, J.: Toxoplasmosebehandlung im Säuglings- und Kindesalter, Monatschr. Kinderh. **100:** 73-79, March, 1952.

7687. Bamatter, F.: Neurer Gesichtspunkte in der Toxoplasmoseforschung, Wien. klin. Wchnschr. **64:** 185-189, March 14, 1952.

7688. Wildi, E.: Quelques problèmes anatomiques d'actualité en neuropathologie du premier âge, Ann. paediat. **178:** 318-332, May/June, 1952.

Tuberculosis 7689. Horton, R., et al.: Epidemic of tuberculosis in a high school, J. A. M. A. **149:** 331-334, May 24, 1952.

See No. 7603.

Tuberculosis, BCG 7690. Aronson, J. D., & Aronson, C. F.: Appraisal of protective value of BCG vaccine, J. A. M. A. **149:** 334-343, May 24, 1952.

7691. Palmer, C. E.: BCG vaccination and tuberculin allergy, Lancet **1:** 935-940, May 10, 1952.

7692. Czermak, H.: Die BCG-impfung bei Neugeborenen, Wien. klin. Wchnschr. **64:** 281-283, April 18, 1952.

7693. Linneweh, F., & Luther, H.: BCG-revaccination, Monatschr. Kinderh. **100:** 83-86, March, 1952.

7694. Wallgren, A. J.: BCG vaccination, advances in Pediatrics **5:** 232-260, Year Book Publishers, 1952.

Tumors 7695. Koh, N. K., et al.: Malignant neoplasms in children, Univ. of Michigan Hospital admissions 1943 through 1947, Univ. Michigan M. Bull. **18:** 123-138, April, 1952.

Tumor, Adrenal 7696. Case report—Unexplained pyrexia in a child, Bristol Med.-Chir. J. **69:** 60-63, April, 1952.

7697. Hawfield, H. H., & Daisley, G. W., Jr.: A report of a case of a functional adrenal ganglioneuroma, Clin. Proc. Child. Hosp., Wash., D. C. **8:** 98-105, May, 1952.

Tumor, Brain 7698. Palmer, H. D., & Murphy, E. S.: Expanding intracranial lesions in childhood, J. A. M. A. **149:** 220-227, May 17, 1952.

Tumor, Neck 7699. White, R. R., & Gosselin, R. S.: Teratoma of the neck in a newborn infant, Pediatrics **9:** 565-571, May, 1952.

Tumor, Odontogenic 7700. Stokke, T.: Inductive effect in odontogenic tumor, J. Oslo City Hosp. **2:** 79-88, April, 1952.

Tumor, Ovary 7701. McGill, J. W.: Carcinoma of the ovary in children, Journal-Lancet **72:** 232-234, May, 1952.

Tumor, Sacrococcygeal 7702. Rosselet, P. J.: A propos d'un tératome sacro-coccygien opéré et guéri, Schweiz. med. Wchnschr. **82:** 495-498, May 3, 1952.

Tumor, Thymus 7703. Bigelow, N. H., & Ehler, A. A.: Lipothymoma: an unusual benign tumor of the thymus gland, J. Thoracic Surg. **23:** 528-538, May, 1952.

Ureterocele 7704. Clin. Case No. 683—Ureterocele, Clin. Rep. Child. Mem. Hosp., Chicago, Ill. **10:** 2095-2096, April, 1952.

Urinary Tract 7705. Jawetz, E.: Practical bacteriologic aspects of urinary tract infection, Am. Pract. & Digest. Treat. **3:** 361-364, May, 1952.

Vaccinia 7706. Finn, O. A., et al.: A case of accidental generalized vaccinia, Brit. M. J. **1:** 1067-1069, May 17, 1952.

Verrucae 7707. Hollander, L.: Treatment of warts, GP **5:** 55-59, June, 1952.

Viral Diseases 7708. Pette, H.: Die Klinik der Viruskrankheiten des Nervensystems, Deutsche Ztschr. Nervenh. **167:** 459-481, No. 6, 1952.
See No. 7469.

Vitamins 7709. Mouriquand, G.: Entérocarences vitaminiques et antibiotiques (en particulier chez l'enfant), J. méd. Lyon No. 775: 373-381, Apr. 20, 1952.

Vitamin A 7710. Lewis, J. M., & Cohlan, S. Q.: Comparative toxicity of aqueous and oily preparations of vitamin A, Pediatrics **9:** 589-596, May, 1952.

Vitamin B. See No. 7496.

Vitamin C 7711. Pirani, C. L.: Relation of vitamin C to adrenocortical function and stress phenomena, Metabolism **1:** 197-222, May, 1952.

Vitamin K. See No. 7530.

Volkmann's Contracture 7712. Nisbet, N. W.: Volkmann's ischaemic contracture benefited by muscle slide operation, J. Bone & Joint Surg. **34-B:** 245-247, May, 1952.

Vomiting, Periodic 7713. Cayla, A., et al.: Sur un cas mortel de vomissements périodiques avec acétonémie, Arch. franç. pédiat. **9:** 299-301, No. 3, 1952.

Wolff-Parkinson-White Syndrome 7714. Paul, O., & Harrison, C. J.: Wolff-Parkinson-White syndrome in an infant, J. A. M. A. **149:** 363-364, May 24, 1952.

Vulvovaginitis, Herpetic 7715. Krugman, S.: Primary herpetic vulvovaginitis, Pediatrics **9:** 585-588, May, 1952.

Xeroderma Pigmentosum 7716. Smithers, D. W., & Wood, J. H.: Xeroderma Pigmentosum. An attempt at cancer prophylaxis, Lancet **1:** 945-946, May 10, 1952.

Xerodermosteosis 7717. Bartsocas, S., & Michail, J.: Sur un cas rare de syndrome de Gougerot-Houwers-Sjogren ou xérodermostéose avec développement précoce des organes génitaux et du corps, chez un enfant, Arch. franç. pédiat. **9:** 266-269, No. 3, 1952.

Current Pediatric References

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From the Department of Pediatrics, Marquette University, School of Medicine, Milwaukee, Wis.

Abdomen, Acute 7718. Kahle, H. R.: Acute abdominal emergencies in children, New Orleans M. & S. J. **104**: 429-445, May, 1952.

Abscess, Brain 7719. Farley, D. L. B.: Recovery from a large frontal lobe abscess in infancy in a 6-year-old child, Proc. Roy. Soc. Med. **45**: 400-401, June, 1952.

Abscess, Subtemporal 7720. Heck, W. E., & McNaught, R. C.: Periauricular bacteroides infection, probably arising in the parotid, J. A. M. A. **194**: 662-663, June 14, 1952.

Abscess, Tubo-ovarian 7721. Clin. Case No. 692—Mass in left lower quadrant, Case Reports Child. Mem. Hosp., Chicago, Ill. **10**: 3034-3035, June, 1952.

Acanthrocytosis 7722. Singer, K., et al: Acanthrocytosis. A genetic erythrocytic malformation, Blood **7**: 577-591, June, 1952.

Acidosis 7723. Natelson, S., & Barbour, J. H.: Equation and nomogram for approximation of alkali requirements in acidosis, Am. J. Clin. Path. **22**: 426-439, May, 1952.

ACTH 7724. Pickering, G. W.: Allergy and ACTH, Brit. M. J. **1**: 1207-1210, June 7, 1952.

7725. Brown, E. A.: ACTH and allergy, Ann. Allergy **10**: 356-391, May/June, 1952.

7726. Marie, J., & Cruciani, C.: Cortisone et ACTH en pédiatrie, Presse méd. **60**: 829-834, June 4, 1952.

See Nos. 7769, 7770, 7777, 7974, 7980, and 8013.

Adolescence. See No. 7923.

Adrenogenital Syndrome. See No. 8026.

Aerosols 7727. Miller, J. B., & Boyer, E. H.: A nontoxic detergent for aerosol use in dissolving viscid bronchopulmonary secretions, J. Pediat. **40**: 767-771, June, 1952.

Amaurotic Family Idiocy 7728. Rayner, S.: Juvenile amaurotic idiocy, Acta genetica et statistica medica **3**: 1-5, No. 1, 1952.

Anemia, Aplastic 7729. Veeneklaas, G. M. H.: Aplasia of the bone marrow: a new cause of the Von Jaksch syndrome, Arch. Dis. Childhood **27**: 134-138, April, 1952.

Anemia, Hemolytic 7730. Zinkham, W. H., & Diamond, L. K.: In vitro erythrophagocytosis in acquired hemolytic anemia, Blood **7**: 592-601, June, 1952.

Anemia, Hypoplastic 7731. Anderson, D. E.: Chronic regenerative anaemia of the newborn, M. J. Australia **1**: 573-576, Apr. 26, 1952.

Anemia, Macrocytic (Goat's Milk) 7732. Boissonnas, L., et al.: Anémie au lait de chèvre, Rev. méd. Suisse Rom. **72**: 323-332, May, 1952.

Anemia, Mediterranean 7733. Shapiro, I., et al: Splenectomy in two Chinese siblings with Mediterranean anemia, New York State J. Med. **52**: 1426-1430, June 1, 1952.

Anemia, Megaloblastic 7734. Baker, S. J. & Sinn, H. J.: Megaloblastic anaemia of infancy: report of a case, M. J. Australia **1**: 750-752, May 31, 1952.

7735. Rickards, A. G.: Megaloblastic anaemia of infancy, Brit. M. J. **1**: 1226-1227, June 7, 1952.

Anesthesia 7736. Van Nouhuys, F.: Pentothal-nitrous oxide-oxygen anaesthesia with curare for tonsillectomy, Arch. chir. neerl. **4**: 95-99, No. 2, 1952.

Aneurysm, Aorta 7737. Mitchell, R. G., & Claireaux, A. E.: Mycotic aneurysm of the abdominal aorta, Arch. Dis. Childhood **27**: 147-152, April, 1952.

Angiography, Cerebral 7738. Picaza, J. A.: Cerebral angiography in children, J. Neurosurg. **9**: 235-244, May, 1952.

Anomalies 7739. Geyer, H.: Dysplasmatisch-idiotische kinder Ovariell insuffizienter Mutter, Arch. f. Gynäk. **181:** 277-289, No. 3, 1952.

7740. Olim, C. B., & Turner, H. B.: Anencephaly in fetuses of mother with tetralogy of Fallot, J. A. M. A. **149:** 932-933, July 5, 1952.

Anomalies, Anorectal 7741. Pinto, V. A. de C., & Moraes, R. de V.: The abdominoperineal approach in the treatment of anorectal anomaly: technical considerations, J. Internat. Coll. Surgeons **17:** 488-491, April, 1952.

Anomalies, Brain 7742. Zellweger, H.: Agenesia corporis callosi, Helvet. paediat. acta **7:** 136-155, April, 1952.

Anomalies, Coronary Artery 7743. Keizer, D. P. R., & Rochat, R. R.: Anomalous origin of left coronary artery, Am. J. Dis. Child. **83:** 769-773, June, 1952.

Anomalies, Extremities 7744. Inglis, K.: The nature of agenesis and deficiency of parts, Am. J. Path. **28:** 449-476, May-June, 1952.

Anomalies, Fetal 7745. El Sherbini, R. M.: A case of foetal abnormality that produced acute inversion of the uterus, J. Obst. & Gynaec. Brit. Emp. **59:** 408, June, 1952.

Anomalies, G. U. Tract 7746. Williams, D. I.: The diagnosis of intersex, Brit. M. J. **1:** 1264-1270, June 14, 1952.

Anomalies, Multiple. See No. 7744.

Anomalies, Nose 7747. Johnson, G. E.: Congenital atresia of the nasal choanae, J. M. A. Alabama **21:** 357-360, June, 1952.

Anomalies, Skeletal 7748. Zellweger, H., et al: Ueber einen Fall von Kraniostenose mit multiplen Epiphysenstörungen und Luxationen, Helvet. paediat. acta **7:** 185-192, April, 1952.

Anomalies, Skull 7749. O'Rahilly, R.: Anomalous occipital apertures, J. Mt. Sinai Hosp. **19:** 509-519, May-June, 1952.

Antibiotics 7750. Herrell, W. E.: Current trends in antibiotic therapy, J. Iowa M. Soc. **42:** 287-292, July, 1952.

7751. Eisenberg, G. M., & Wagner, B. M.: Bacterial susceptibility to antibiotics. 2. Determination by means of a standardized, routine procedure having clinical significance, Am. J. M. Sc. **223:** 600-606, June, 1952.

7752. Bartell, P.: Interference of aureomycin with the activity of penicillin in vivo, J. Infect. Dis. **90:** 273-278, May-June, 1952.

See No. 7900.

Aorta, Abdominal Coarctation 7753. Fisher, E. R., & Corcoran, A. C.: Congenital coarctation of the abdominal aorta with resultant renal hypertension, Arch. Int. Med. **89:** 943-950, June, 1952.

Appendicitis 7754. Dennison, W. M., & MacPherson, D. A.: Acute appendicitis in the young child, Glasgow M. J. **33:** 175-184, May, 1952.

Arachnodactyly 7755. Perritt, R. A.: Marfan's syndrome. Ectopia lentis with general deformities, J. Internat. Coll. Surgeons **17:** 217-219, Feb. 1952.

Arterial Occlusion. See No. 7842.

Arthritis, Hip. 7756. Tiscornia, R. E.: El signo del obturador. Su utilidad en el diagnostico precoz de las artritis de la cadera en los niños, Arch. pediat. Uruguay **23:** 245-251, April, 1952.

Asthma 7757. Bates, D. V.: Impairment of respiratory function in bronchial asthma, Clin. Sc. **11:** 203-207, May, 1952.

7758. Rackemann, F. M., & Edwards, M. C.: Asthma in children. (Conclusion), New England J. Med. **246:** 858-863, May 29, 1952.

Asthma, Infectious 7759. Mueller, H. L., & Flake, C. G.: Irradiation of the nasopharynx in children with infectious asthma, New England J. Med. **246:** 924-927, June 12, 1952.

Atlanto-axial Dislocation 7760. Kennelly, J. M., Jr.: A report of a case of atlanto-axial dislocation in a Mongol, Proc. Staff. Meet., Mayo Clin. **8:** 142-145, June, 1952.

BAL. See No. 7946.

Bladder, Exstrophy 7761. Sanchez R. P.: Extrofia vesical degenerada, J. Internat. Coll. Surgeons **17:** 528-533, April, 1952.

Blood, formation of 7762. Gairdner, D., et al.: Blood formation in infancy. Part 1. The normal bone marrow, Arch. Dis. Childhood **27:** 128-133, April, 1952.

Bonnevie-Ullrich Syndrome. See Pterygium colli.

Breast Feeding 7763. Miller, R. A.: Factors influencing lactation, Arch. Dis. Childhood **27:** 187-204, April, 1952.

Breast Milk 7764. Mautner, H.: The transfer of drugs into the milk, J. Mt. Sinai Hosp. **19:** 80-83, May-June, 1952.

Bronchiectasis 7765. Valledor, T., & Navarrete, A.: Bronchiectasis in childhood and adult pulmonary tuberculosis, Dis. Chest **22:** 46-54, July, 1952.

Brucellosis 7766. Herrell, W. E., & Barber, T. E.: Treatment of brucellosis with aureomycin or terramycin combined with dihydrostreptomycin, Postgrad. Med. **11:** 476-486, June, 1952.

7767. Victor, J., et al: Human blood opsonin titers against brucella, J. A. M. A. **149:** 809-813, June 28, 1952.

7768. Spink, W. W., et al: Diagnostic criteria for human brucellosis, J. A. M. A. **149:** 805-808, June 28, 1952.

Burns 7769. Trusler, H. M., et al.: An evaluation of pituitary adrenocorticotropic hormone (ACTH) in the treatment of severe burns: relationship to skin grafting, Plast. Reconstruct. Surg. **9**: 478-489, May, 1952.

7770. McNichol, J. W.: Experience with a case of simultaneous autograft and homograft of skin in third degree burns on **ACTH,** Plast. & Reconstruct. Surg. **9**: 437-472, May, 1952.

7771. Bernstein, R. E.: Burns. 2. Fluid therapy in relation to burn shock, South African M. J. **26**: 416-421, May 17, 1952.

7772. Gissane, W., & Jackson, D.: The principles of the treatment of burns, Ann. Roy. Coll. Surgeons England **10**: 357-368, June, 1952.

Celiac Disease 7773. Larue, A.: Uns cas de maladie coeliaque, Laval med. **17**: 625-629, May, 1952.

Cerebral Edema 7774. Altegoer, E.: Zur Morphologie und Genese des akuten Hirnödems bei ernährungsgestörten Säuglingen, Beitr. path. Anat. **112**: 205-215, No. 2, 1952.

Cerebral Hemorrhage 7775. Bradley, K. C.: Extra-dural haemorrhage, Australian & New Zealand J. Surg. **21**: 241-260, May 1952.

Cerebral Palsy 7776. Benda, C. E.: Part 2. Cerebral palsy, birth injuries and anoxia: Developmental Disorders of Mentation and Cerebral Palsies, New York, 1952, Grune & Stratton, pp. 221-544.

Chloromycetin. See Nos. 7896, 7901, 7987, and 7992.

Chorea 7777. Dixon, A. St. J., & Bywaters, E. G. L.: Methods of assessing therapy in chorea with special reference to the use of ACTH, Arch. Dis. Childhood **27**: 161-166, April, 1952.

Cirrhosis, Liver 7778. Clin. Case No. 691. Cirrhosis of the liver, Case Reports Child. Mem. Hosp., Chicago, Ill. **10**: 3029-3033, June, 1952.

7779. Bhalla, A. S.: Infantile hepatic cirrhosis, Antiseptic **49**: 382-384, May, 1952.

Cleft Palate 7780. Slaughter, W. B., & Phair, G. M.: A complete cleft palate program, J. Speech & Hearing Disorders **17**: 123-128, June 1952.

7781. Figi, F. A.: The repair of secondary cleft lip and nasal deformity, J. Internat. Coll. Surgeons **17**: 297-305, March, 1952.

7782. Kitlowski, E. A.: Operative technic for reconstruction of the traumatized palate, J. Internat. Coll. Surgeons **17**: 695-709, May, 1952.

7783. Le Mesurier, A. B.: The treatment of complete unilateral harelips, Surg., Gynec. & Obst. **95**: 17-27, July, 1952.

Clubfoot 7784. Taillard, W.: Le traitement du pied bot par la methóde de J. H. Kite, Rev. méd. Suisse Rom. **72**: 305-313, May, 1952.

Collagen Diseases. See No. 7973.

Cortisone. See Nos. 7726, 7847, 7974, 7987, and 8050.

Coxa Plana 7785. Kite, J. H. & French, G. O.: The early diagnosis of flat-headed femur, South. M. J. **45**: 581-585, July, 1952.

Cretinism 7786. Mullinger, M., et al: Cretinism, Canad. M. A. J. **66**: 560-562, June, 1952.

Cyst, Intracranial 7787. Palma, E. C.: Quiste hidatico intracraneano en el niño, Arch. pediat. Uruguay **23**: 235-244, April, 1952.

Cyst, Lung 7788. Cooke, F. N., & Blades, B.: Cystic disease of the lungs, J. Thoracic Surg. **23**: 546-569, June 1952.

7789. Kate, J. T., & Dicke, W. K.: Congenital pulmonary cysts in infants, Arch. chir. neerl. **4**: 145-154, No. 2, 1952.

7790. Susman, M. P.: Hydatid cyst of the lung, Australian & New Zealand J. Surg. **21**: 297-299, May, 1952.

7791. Bredt, H.: Lymphangiectasia pulmonum congenita, Virchows Arch. path. Anat. **321**: 517-530, No. 5, 1952.

Cyst, Mediastinal 7792. Steckler, C., et al: Primary mediastinal cystic hygroma (cystic lymphangioma), New York State J. Med. **52**: 1440-1442, June, 1, 1952.

Cyst, Mesentery 7793. Moore, T. C.: Congenital cysts of the mesentery, Quart. Bull. Indiana Univ. Med. Cent. **14**: 36-40, April, 1952.

Cyst, (Myxomatous) Wrist 7794. Pearce, A. E., et al.: Recurrent myxomatous cyst of the skin, Arch. Surg. **64**: 835-839, June, 1952.

Cystine Storage Disease 7795. Bickel, H., & Smellie, J. M.: Cystine storage disease with amino-aciduria, Lancet **1**: 1093-1095, May 31, 1952.

Dermatitis, Ammoniacal 7796. Stephens, L. J., et al.: o-Benzyl-p-chlorophenol in the prevention and treatment of ammonia dermatitis, J. Pediat. **40**: 750-756, June, 1952.

Dermatomyositis 7797. Brimblecombe, F. S. W., & Keech, M.: Presumed dermatomyositis with cardiomegaly, trichiniasis and epilepsy, Proc. Roy. Soc. Med. **45**: 398-399, June, 1952.

Diabetes 7798. Wagner, R.: Problems in juvenile diabetes mellitus, J. Mt. Sinai Hosp. **19**: 249-255, May-June, 1952.

Diaphragm, Defects 7799. Ravitch, M. M., & Handelsman, J. C.: Defects in right diaphragm of infants and children with herniation of liver, Arch. Surg. **64**: 794-802, June, 1952.

Diarrhea, Epidemic 7800. Sharpe, M. E.: Group D streptococci in the faeces of healthy infants and of infants with neonatal diarrhoea, J. Hyg. **50**: 209-228, June, 1952.

Diarrheal Diseases 7801. Alexander, M. B., et al.: Streptomycin treatment of infantile diarrhoea and vomiting, J. Hyg. **50**: 246-264, June, 1952.

7802. Hallman, N.: Effect of potassium therapy in severe infantile gastroenteritis, Acta paediat. **41**: 238-248, May, 1952.

7803. Dupont, A., & Keiser-Nielsen, H.: Escherichia coli 55: B5:6 in intestinal canal of infants treated with lactobacillin milk ("lacto-Y-48"), Acta paediat. **41**: 222-228, May, 1952.
See No. 7774.

Duodenal Obstruction 7804. Dey, D. L.: Acute duodenal obstruction due to an intramural haematoma, M. J. Australia **1**: 708, May 24, 1952.

Dysostosis, Cleidrocranial 7805. Hausmann, E., & Seyss, R.: Zur abortiven Form der Mutationsdysostose (Dysostosis cleidocranialis), Helvet. paediat. acta **7**: 193-201, April, 1952.

Dysostosis, Mandibulofacialis, 7806. O'Connor, G. B., & Conway, M.: Treacher Collins syndrome (dysostosis mandibulofacialis), J. Internat. Coll. Surgeons **17**: 714-717, May, 1952.

Dysplasia, Ectodermal 7807. James, T., Ectodermal dysplasia, Acta paediat. **41**: 229-237, May, 1952.

Dysplasia, Epiphysialis Multiplex 7808. Nohe, P. C., & Garceau, G. J.: Dysplasia epiphysialis multiplex, Quart. Bull. Indiana Univ. Med. Cent. **14**: 31-35, April, 1952.

Dysplasia, Fibrous. See No. 8002.

Ectopia Cordis 7809. Wilson, E. J.: A case of ectopia cordis surviving nine hours, Brit. M. J. **1**: 1175-1176, May 31, 1952.

Eczema Vaccination 7810. Hoffman, I. L.: Atypical eczema vaccinatum, U. S. Armed Forces M. J. **3**: 885-890, June, 1952.

Electrocardiography 7811. Courjon, J.: Étude électro-clinique des absences de l'enfant, Pédiatrie **41**: 383-399, No. 3, 1952.

7812. Chaptal, J., et al.: Donnees nouvelles sur l'électroencephalographie au cours de la méningite tuberculeuse de l'enfant traitée par la streptomycine, Pédiatrie **41**: 315-343, No. 3, 1952.

Electroencephalography 7813. Turner, M.: Interpretacion de los datos electroencefalograficos en las encefalopatias infantiles, Arch. pediat. Uruguay **23**: 165-170, March, 1952.

Encephalitis 7814. Barrett, A. M., et al.: An outbreak of encephalitis, possibly due to poliomyelitis virus, Brit. M. J. **1**: 1317-1322, June 21, 1952.

Encephalitis Periaxialis Diffusa 7815. Sarma, A. V. S.: Schilder's disease (encephalitis periaxialis diffusa), Antiseptic **49**: 290-293, April, 1952.

Encephalitis, Postvaccinal 7816. Bickers, D. S.: Postvaccinal encephalitis with pre-existing focal cerebral seizures, New England J. Med. **246**: 929-931, June 12, 1952.

Encephalitis, Western Equine 7817. Fulton, J. S., & Burton, A. N.: Human encephalitis in Saskatchewan caused by the virus of western equine encephalomyelitis, Canad. J. Pub. Health **43**: 212-220, May, 1952.

Endocarditis, Bacterial 7818. Jones, H. E., & Dolton, E. G.: Bacterial endocarditis after a Taussig-Blalock operation in a case of unusual pathology, Arch. Dis. Childhood **27**: 157-160, April, 1952.
See No. 7854.

Endocarditis, Mycotic 7819. Kunstadter, R. H., et al.: Mycotic endocarditis due to Candida albicans, J. A. M. A. **149**: 829-832, June 28, 1952.

Endocrinology 7820. Talbot, N. B., et al.: Functional endocrinology. From birth to adolescence, Cambridge, Mass., 1952, Harvard University Press, pp. 1-584.

Enuresis 7821. Seiger, H. W.: Treatment of essential nocturnal enuresis, J. Pediat. **40**: 738-749, June, 1952.

Eosinophilic Granuloma 7822. Dingley, A. R.: Eosinophil granuloma of the temporal bone, J. Laryng. & Otol. **66**: 285-287, June, 1952.

Epilepsy 7823. Lund, M.: Epilepsy in association with intracranial tumour, Acta psychiat. et neurol. supp. **81**: 14-149, 1952.

7824. Davidson, D. T.: The medical management of epilepsy, Delaware State M. J. **24**: 147-152, June, 1952.

7825. Allen, I. M.: Forced thinking as part of the epileptic attack, New Zealand M. J. **51**: 86-95, April, 1952.

Epiphysis, Slipped 7826. Eppright, R. H., & Boylston, B. F.: Multiple slipped femoral epiphyses, Surgery **31**: 928-932, June, 1952.

Epispadias 7827. Campbell, M.: Epispadias: a report of fifteen cases, J. Urol. **67**: 988-999, June, 1952.

Erythroblastosis Fetalis 7828. Flynn, J. E.: Possible prevention of anti-A isosensitization disease. By desensitization of the mother with substance A, Am. J. Clin. Path. **22**: 418-423, May, 1952.

7829. Phansomboon, S., & Pollak, O. J.: A Study on the A factor as a cause of haemoloytic disease in premature babies, Brit. M. J. **1**: 1170-1172, May 31, 1952.

7830. Tieche, H. L.: Erythroblastosis fetalis, West. J. Surg. **60**: 280-287, June, 1952.

7831. Pettenkofer, H.-J.: Ueber die Häufigkeit der Iso-immunisierung während der Schwangerschaft und ihre Bedeutung für das Entstehen einer fetalen Erythroblastose, Arch. f. Gynäk. **181**: 325-340, No. 3, 1952.

See No. 7977.

Esophagus 7832. Thorek, P.: Recent trends in esophageal surgery, Dis. Chest **22**: 33-45, July, 1952.

Eye, Lens, Dislocated 7833. Spaeth, E. B.: Surgery of dislocated lenses in children, J. Internat. Coll. Surgeons **17**: 201-207, Feb., 1952.

Fat Absorption. See 7963.

Feeding 7834. Waldron, R. J., & Fries, J. H.: Comparative value of a syrup of dehydrated banana as a carbohydrate for infant feeding, Arch. Pediat. **69**: 205-211, May, 1952.

7835. Leverton, R. M., et al.: Further studies of the use of meat in the diet of infants and young children, J. Pediat. **40**: 761-766, June, 1952.

7836. Deem, H.: A revised system of feeding, New Zealand M. J. **51**: 118-119, April, 1952.

7837. La Pointe, D., et al.: Étude clinique comparative de deux formules de lait, Laval méd. **17**: 618-624, May, 1952.

Feet 7838. Craigmile, D. A.: The effects of faulty footwear in children, Presse méd. **227**: 592-596, June 18, 1952.

Fluids 7839. Edelman, I. E., et al.: Further observations on total body water; 1. Normal values throughout the life span, Surg., Gynec. & Obst. **95**: 1-12, July, 1952.

Fluoridation. See No. 8007.

Foreign Body, Esophagus 7840. Lau, R. H. F.: Clinico-pathological conference, Clin. Proc. Child. Hosp. Wash. D. C. **8**: 146-149, June, 1952.

Fractures 7841. Hammond, G.: The management of supracondylar fractures of the humerus in children, S. Clin. North America, pp. 747-762, June, 1952.

Gangrene, Spontaneous 7842. Stokes, G. E., & Shumacker, H. B., Jr.: Spontaneous gangrene in infancy, Angiology **3**: 226-237, June, 1952.

Gastrointestinal Tract, Surgery 7843. Lockard, V. M.: Lesions of the upper gastrointestinal tract in infants and children, Radiology **58**: 696-704, May, 1952.

Glutamic Acid. See No. 7910.

Glycogen Disease 7844. Van Creveld, S.: Glycogen disease, Arch. Dis. Childhood **27**: 113-120, April, 1952.

Granulocytopenia 7845. Vrtilek, M. R.: Das Bild der chronischen Granulocytopenie im Kindesalter, Helvet. paediat. acta **7**: 207-228, April, 1952.

Hand-Schüller-Christian Disease 7846. Stafne, E. C.: Dental roentgenologic manifestations of systemic disease, Radiology **58**: 820-829, June, 1952.

7847. Karlén, K-H.: A case of the Hand-Schüller-Christian disease treated with cortisone, Acta paediat. **41**: 282-289, May, 1952.

Head, Injuries 7848. Campbell, E., & Whitefield, R. D.: Degrees of recovery following prolonged post-traumatic coma, Ann. Surg. **135**: 899-910, June, 1952.

See No. 7866.

Heart 7849. Rushmer, R. F., et al.: Direct-writing heart-sound recorder. (The sonvelograph), Am. J. Dis. Child. **83**: 733-739, June, 1952.

7850. Rushmer, R. F., et al.: Variability in detection and interpretation of heart murmurs. A comparison of auscultation and stethography, Am. J. Dis. Child. **83**: 740-754, June, 1952.

Heart Disease 7851. Maresh, G. J., et al.: Incidence of heart disease among Colorado school children, J. A. M. A. **149**: 802-805, June 28, 1952.

Heart Disease, Congenital 7852. Edwards, J. E., et al.: Congenital malformations of the heart, Lab. Invest. **1**: 197-207, No. 2, 1952.

7853. Bulgarelli, R.: Die axiale transversale Stratigraphie (Querschnittstomographie) beim Studium der angeborenen Herzfehler, Helvet. paediat. acta **7**: 156-179, April, 1952.

7854. Horne, J. N., & Wilson, B. D. R.: Bacterial endocarditis in congenital heart disease, St. Thomas's Rep. **7**: 63-71, 2nd Series, 1951.

7855. Gross, R. E.: Surgical Closure of an aortic septal defect, Circulation **5**: 858-863, June, 1952.

7856. Harris, J. W. S.: A case of congenital heart block. Recognized at the thirty-eighth week of pregnancy, J. Obst. & Gynaec. Brit. Emp. **59**: 404-405, June, 1952.

7857. Jönsson, G., & Saltzman, G-F.: Infundibulum of the patent ductus arteriosus studied by thoracic aortography, Acta radiol. **37**: 445-451, May, 1952.

7858. Brock, R. C.: Congenital pulmonary stenosis, Am. J. Med. **12**: 706-719, June, 1952.

7859. Brock, R. C.: Direct cardiac surgery in the treatment of congenital pulmonary stenosis, Ann. Surg. **136**: 63-72, July, 1952.

7860. Soulié, P., et al.: Étude physiopathologique post-opératoire de la trilogie de Fallot, Arch. mal. coeur **45**: 385-411, May, 1952.

7861. Hartenstein, Lt. H., & Freeman, D. J.: Origin of the left coronary artery from the pulmonary artery, Am. J. Dis. Child. **83**: 774-781, June, 1952.

Hemangioma, Intestine 7862. Rickham, P. P.: A case of haemangiomatosis of the small intestine, Brit. J. Surg. **39**: 462-463, March, 1952.

Hemangioma, Skin 7863. Brown, J. B., & Fryer, M. P.: Hemangiomas: treatment and repair of defects, Surg., Gynec. & Obst. **95**: 33-44, July, 1952.

Hemangiosarcoma 7864. Kessel, I.: A case of Kaposi's haemangiosarcoma, Arch. Dis. Childhood **27**: 153-156, April, 1952.

Hematoma, Extradural 7865. King, A. B., & Chambers, J. W.: Delayed onset of symptoms due to extradural hematomas, Surgery **31**: 839-844, June, 1952.

7866. Lemmen, L. J., & Schneider, R. C.: Extradural hematomas of the posterior fossa, J. Neurosurg. **9**: 245-253, May, 1952.

Hematoma, Subdural 7867. French, L. A.: Subdural hematomas in infants, Postgrad. Med. **11**: 538-542, June, 1952.

7868. Poppen, J. L. & Strain, R. E.: Chronic subdural hematomas, S. Clin. North America, pp. 791-799, June, 1952.

Hernia, Diaphragmatic 7869. Philipp, E. E., & Skelton, M. O.: Congenital diaphragmatic hernia in siblings, Brit. M. J. **1**: 1283-1284, June 14, 1952.

Hernia, Inguinal 7870. Pinto, V. A. deC.: Inguinal hernia in infants and children, J. Internat. Coll. Surgeons **17**: 729-733, May, 1952.

7871. Duckett, J. W.: Treatment of congenital inguinal hernia, Ann. Surg. **135**: 879-885, June, 1952.

7872. Perrot, A., et al.: Traitement chirurgical de la hernie inguinale de l'enfant et du nourrisson, Rev. méd. Suisse Rom. **72**: 260-267, May, 1952.

Hernia, Umbilical 7873. Crump, E. P., & Robinson, J. M.: Umbilical hernia. 2. Occurrence in Negro adolescents and young adults, J. Pediat. **40**: 777-780, June, 1952.

Herpes Zoster 7874. Feldman, G. V.: Herpes zoster neonatorum, Arch. Dis. Childhood **27**: 126-127, April, 1952.

Hospitalization 7875. Couve, Ph., et al.: Syndromes de carence affective du jeune enfant en collectivité. Essai de traitement, Pédiatrie **41**: 283-297, No. 3, 1952.

Hospitals 7876. Babcock, K. B.: The excessive use of Blue Cross benefits, Hospitals **26**: 49-51, July, 1952.

Hyperpyrexia Pallida 7877. Pickerill, H. P.: Hyperpyrexia pallida and its prevention, Australian & New Zealand J. Surg. **21**: 261-268, May, 1952.

Hypervitaminosis A 7878. Reyersbach, G. C., et al.: Vitamin A intoxication, New England J. Med. **246**: 978-980, June 19, 1952.

Hypospadias 7879. Smith, D. R., & Blackfield, H. M.: A critique on the repair of hypospadias, Surgery **31**: 885-899, June, 1952.

7880. Lipworth, E.: The treatment of hypospadias, South African M. J. **26**: 453-455, May 31, 1952.

7881. Cecil, A. B.: Modern treatment of hypospadias, J. Urol. **67**: 1006-1011, June, 1952.

7882. Burns, E., & Beckman, G. E., Jr.: Evaluation of operations for hypospadias, J. Urol. **67**: 1000-1005, June, 1952.

Immunity Defect. See No. 7895.

Inclusion Disease 7883. Fetterman, G. H.: A new laboratory aid in the clinical diagnosis of inclusion disease of infancy, Am. J. Clin. Path. **22**: 424-425, May, 1952.

Intestine—Microbiology. See No. 7803.

Intestine, Obstruction 7884. Dean, G. O., & Murry, J. W.: Volvulus of the sigmoid colon, Ann. Surg. **135**: 830-840, June, 1952.

7885. Lee, C. M., Jr.: Intestinal obstruction in the newborn infant, J. M. A. Georgia **41**: 233-242, June, 1952.

Iodine, Radioactive. See No. 8014.

Irradiation. See No. 7759.

Jaundice, Obstructive 7886. Clin. Case No. 690: Pruritus with intermittent jaundice, Case Reports Child. Mem. Hosp., Chicago, Ill. **10**: 3027-3029, June, 1952.

Kernicterus 7887. Butler, N. R., & Spector, W. G.: Kernicterus without prematurity or blood-group incompatibility, Brit. M. J. **1**: 1168-1170, May 31, 1952.

Kidney, Polycystic 7888. Path. Case No. 694. Polycystic kidneys, Case Reports Child. Mem. Hosp. Chicago, Ill. **10**: 3040-3042, June, 1952.

Kyphosis 7889. Rocher, H.-L.: L'appareillage des insuffisances at déformations thoraciques: la brassière orthopédique Spitzy-Rocher, Rev. orthop. **38:** 196-199, Apr.-June, 1952.

Laryngoscopy 7890. Emerson, E. B.: A catheterizing laryngoscope for tracheobronchial aspiration of the newborn and premature infant, Am. J. Obst. & Gynec. **63:** 1374-1376, June, 1952.

Laryngo-tracheitis 7891. McSweeney, C. J.: Acute laryngo-tracheitis of children, Irish J. M. Sc. No. 318: 254-262, June, 1952.

Letterer-Siwe Disease 7892. McLetchie, N. G. B.: Unusual histiocytic reaction to lymph nodes in Letterer-Siwe disease, Am. J. Clin. Path. **22:** 520-534, June, 1952.

Leukemia, Myeloblastic 7893. Casilli, A. R., et al.: Acute neonatal myeloblastic leukemia, Am. J. Dis. Child. **83:** 788-793, June, 1952.

Lignac's Disease. See Cystine storage disease.

Liver, Herniation. See No. 7799.

Lobstein's Syndrome. See Osteogenesis imperfecta.

Malnutrition 7894. Aceto, G., & Limoli, S.: Innesti placentari alla filatov nelle malattie della nutrizione, Pediatria **60:** 145-152, No. 3-4, 1952.

Measles 7895. Thamdrup, E.: Re-infections with measles. Familial immunity defect, Acta paediat. **41:** 276-282, May, 1952.

7896. Del Principe, A., & Della Cava, F.: Considerazioni sull' impiego del cloramfenicolo nel morbillo, Pediatria **60:** 168-188, No. 3-4, 1952.
See Nos. 7906 and 7972.

Meckel's Diverticulum 7897. Case Record Mass. Gen. Hosp.: presentation of a case, New England J. Med. **246:** 985-987, June 19, 1952.

Mediterranean Exanthematic Fever 7898. Cartagenova, L., & Agnese, A.: La febbre esantematica mediterranea, Pediatria **60:** 153-159, No. 3-4, 1952.

Megacolon 7899. Adams, H. D.: Megacolon: a contrast of results of two methods of surgical management, S. Clin. North America, pp. 917-922, June, 1952.

Meningitis. See No. 8001.

Meningitis, Influenzal 7900. Lepper, M. H., et al.: Treatment of hemophilus influenzae meningitis, Am. J. Dis. Child. **83:** 763-768, June, 1952.

7901. Grönroos, J. A..: On the activity of chloramphenicol against Haemophilus influenzae with special reference to influenzal meningitis, Acta paediat. **41:** 249-259, May, 1952.

Meningitis, Tuberculous 7902. Ruziczka, O.: Tuberculous meningitis, J. Pediat. **40:** 708-713, June, 1952.

7903. Robertson, F., & Gairdner, D.: The results of treatment of tuberculous meningitis with streptomycin, Lancet **1:** 1176-1180, June 14, 1952.

7904. Ravreby, L., et al.: The antibiotic therapy of tuberculous meningitis, New England J. Med. **246:** 883-890, June 5, 1952.

7905. Perry, T. L.: Treatment of tuberculous meningitis in children, J. Pediat. **40:** 687-707, June, 1952.

7906. Akkoyunlu, A.: Die Wirkung der Masern auf die in Streptomycinbehandlung befindliche Meningitis tuberculosa, Helvet. paediat. acta **7:** 180-184, April, 1952.

7907. Debré, R., et al.: Bacilles résistants a la streptomycine dans la méningite tuberculeuse, Semaine hôp. Paris **28:** 1676-1683, May 30, 1952.
See No. 7812.

Meningitis, Virus 7908. Assmann, H.: Bericht über eine Epidemie von Virusmeningitis, Deutsche med. Wchnschr. **7:** 740-741, June 6, 1952.

Mental Deficiency 7909. Benda, C. E.: Part 1. The inadequacy of present-day concepts of mental deficiency and mental illness. Developmental Disorders of Mentation and Cerebral Palsies, New York, 1952, Grune & Stratton, pp. 1-217.

7910. Zabarenko, R. N., & Chambers, G. S.: An evaluation of glutamic acid in mental deficiency, Am. J. Psychiat. **108:** 881-887, June, 1952.

Mongolism 7911. Kaplan, I. I.: X-ray therapy of mongolism, Arch. Pediat. **69:** 199-204, May, 1952.

Mortality, Infant 7912. Johnson, D. L.: Maternal and infant mortality in a rural hospital, Minnesota Med. **35:** 550-554, June, 1952.

7913. Symposium—Semaine hôp. Paris **28:** 1807-1816, June 10, 1952.
See No. 7965.

Muscular Dystrophy 7914. Lightwood, R.: Congenital limitation of joint movement with subsequent progressive muscular dystrophy, Proc. Roy. Soc. Med. **45:** 397-398, June, 1952.

Nephrocalcinosis 7915. Lightwood, R.: Idiopathic hypercalcaemia with failure to thrive: nephrocalcinosis, Proc. Roy. Soc. Med. **45:** 401, June, 1952.

Neurofibromatosis 7916. Preston, F. W., et al.: Cutaneous neurofibromatosis (von Recklinghausen's disease), Arch. Surg. **64:** 813-827, June, 1952.

Neuromyelitis Optica 7917. Scott, G. I.: Neuromyelitis optica, Am. J. Ophth. **35:** 755-764, June, 1952.

Newborn 7918. Brown, J. J. M.: Surgical aspects of vomiting in the newborn, Edinburgh M. J. **59:** 51-62, June, 1952.

7919. Parmelee, A. H.: Management of the newborn, Chicago, 1952, Year Book Publishers, Inc., 343 pp.

7920. Leahy, L. J., & Herrmann, J. W.: Respiratory emergencies in the newborn, Postgrad. Med. **11:** 543-548, June, 1952.

7921. Koop, C. E.: Certain aspects of surgery of the newborn, Delaware State M. J. **24:** 152-157, June, 1952.

See Nos. 7800, 7874, 7885, 7890, 7893, 7952, 7977, 7984.

Nose, Trauma 7922. Goldman, I. B.: The maxillofacial triad and its correction, with special reference to the nasal septum, J. Internat. Coll. Surgeons **17:** 167-180, Feb., 1952.

Nutrition 7923. Saunders, J. P., et al.: Relation of serum cholinesterase to nutritional status of adolescents, J. Nutrition **47:** 191-201, June 10, 1952.

Ombredanne's Syndrome. See Hyperpyrexia pallida.

Orthodontia 7924. Swanson, L. T.: Objectives and limitations of orthodontic therapy, New England J. Med. **246:** 1007-1012, June 26, 1952.

7925. Freeman, H. D.: Orthodontics in the school dental clinic, Pub. Health **55:** 145-150, June, 1952.

Osteochondrosis Dissecans 7926. Novotny, H.: Osteochondrosis dissecans in two brothers. The pre- and developed state, Acta radiol. **37:** 493-497, May, 1952.

Osteogenesis Imperfecta 7927. Millán, J. M., & Toce, A.: Enfermedad de Lobstein, Semana méd. **100:** 693-699, May 29, 1952.

7928. Sowers, J. A.: Osteogenesis imperfecta, Proc Staff Meet., Mayo Clin. **8:** 133-137, June, 1952.

Otitis 7929. Gianelli, C., and Peluffo, E.: La otoantritis del lactante distrofico, Arch. pediat. Uruguay **23:** 222-234, April, 1952.

7930. Kroath, F., & Quaiser, K.: Otitis media und Säuglingsdyspepsie, Wien. med. Wchnschr. **102:** 401-403, May 24, 1952.

Pancreas, Cystic Fibrosis 7931. Werthemann, A., et al.: Zur Pathogenese der cystischen Pankreasfibrose, Virchows Arch. path. Anat. **321:** 411-457, No. 5, 1952.

7932. Lloyd, M. S., & Robitzek, E. H.: Pneumonectomy for suppurative disease in cystic fibrosis of the pancreas and lung, Quart. Bull. Sea View Hosp. **13:** 114-124, April, 1952.

Para-aminosalicylic Acid 7933. Kniest, W.: Schwere allergische Reaktionen gegen p-Aminsalizylsäure, Deutsche med. Wchnschr. **77:** 676-677, May 23, 1952.

Parasites, Intestinal 7934. James, T.: A case of triple infestation with Trichuris trichuria, Ascaris lumbricoides and Enterobius vermicularis, Glasgow M. J. **33:** 188-189, May, 1952.

Parotitis, Epidemic 7935. Racca, G.: Sul trattamento della parotite epidemica con acido paraminobenzoico, aureomicina chloramfenicolo e terramicina, Minerva med. 43: 931-940, May 3, 1952.

Parotitis, Suppurative 7936. White, R. H. R.: Acute suppurative parotitis in the newborn, Brit, M. J. **1:** 1232, June 7, 1952.

Penicillin 7937. Wylie-Smith, R.: Reaction to penicillin, Lancet **1:** 1211, June 14, 1952.

See No. 7998.

Pituitary, Hypofunction 7938. Hubble, D.: The course of anterior hypopituitarism, Lancet **1:** 1123-1131, June 7, 1952.

Pityriasis Rubra Pilaris 7939. Webster, J. R., & Falk, A. B.: Pityriasis rubra pilaris, Arch. Dermat. & Syph. **65:** 685-700, June, 1952.

Pneumography, Retroperitoneal 7940. Carrara, N., & Maresi, C.: Il retroneumoperitoneo nella diagnostica addominale del bambino, Pediatria **60:** 137-144, No. 3-4, 1952.

Pneumonia 7941. Finke, W.: Childhood pneumonia, a common cause of bronchopulmonary disease, Am. J. Dis. Child. **83:** 755-762, June, 1952.

7942. Köttgen, U., & Grosse-Perdekamp, B.: Zur Behandlung kindlicher Bronchopneumonien, Deutsche med. Wchnschr. **77:** 701-704, May 30, 1952.

Pneumonia, Aspiration 7943. Mahaim, Ch.: Bronchopneumonie par aspiration de farine antidiarrhéique, Schweiz. med. Wchnschr. **82:** 615-618, June 7, 1952.

Pneumonia, Lipoid 7944. Donnelly, L. C., & Hecht, B. P.: Chemical examination of lung tissue for mineral oil, Am. J. Clin. Path. **22:** 449-451, May, 1952.

Poisoning, Lead 7945. Zak, F. G., & Finkelstein, W. E.: Plumbism in children, J. Mt. Sinai Hosp. **19:** 352-358, May-June, 1952.

Poisoning, Mercury 7946. Engelson, G., & Herner, T.: Alkyl mercury poisoning. Acta paediat. **41:** 289-294, May, 1952.

Poisoning, Salicylates 7947. Shannon, W. R.: Aspirin poisoning in children, Minnesota Med. **35**: 555, June, 1952.

Poliomyelitis 7948. Cameron, D.: Discussion on infantile paralysis, Proc. Roy. Soc. Med. **45**: 380-383, June, 1952.

7949. Symposium—Physical therapy, Phys. Therapy Rev. **32**: 339-369, July, 1952.

7950. McCloskey, B. P.: Residual paralysis after poliomyelitis following recent inoculation, Lancet **1**: 1187-1189, June 14, 1952.

7951. Baumeister, J., et al.: The use of tracheotomy, intermittent positive pressure and sedation in the treatment of children ill with poliomyelitis, J. Kansas M. Soc. **53**: 280-284, June, 1952.

7952. Johnson, J. F., & Stimson, P. M.: Clinical poliomyelitis in the early neonatal period, J. Pediat. **40**: 733-737, June, 1952.

7953. Stimson, P. M.: Home care of patients with acute poliomyelitis J. A. M. A. **149**: 719-721, June 21, 1952.

7954. Pollock, L. J., et al.: Absence of clinical evidence of destructive lesions of the sympathetic nervous system in acute anterior poliomyelitis, Arch. Neurol. & Psychiat. **67**: 725-736, June, 1952.

7955. Cioffari, M. S.: Poliomyelitis and injections, J. Michigan M. Soc. **51**: 727-729, June, 1952.

7956. Moore, E. W.: The fate of the face in poliomyelitis, Lancet **1**: 1092-1093, May 31, 1952.

7957. McConnell, A. A.: Poliomyelitis in infants under the age of 6 months, Arch. Dis. Childhood **27**: 121-125, April, 1952.

7958. Ferris, B. G., Jr., et al.: Pulmonary function in convalescent poliomyelitic patients, New England J. Med. **246**: 919-923, June 12, 1952.
See No. 7814.

Potassium Deficiency 7959. Lo Presti, J. M., et al.: Potassium deficiency, Clin. Proc. Child. Hosp., Wash. D. C. **8**: 138-141, June, 1952.

Prematurity 7960. Ferguson, A. E., et al.: Some circumstances affecting the survival of premature children, Glasgow M. J. **33**: 143-174, May 1952.

7961. Belford, W. W.: Prematurity from the standpoint of the pediatrician, West. J. Surg. **60**: 249-258, June, 1952.

7962. Traut, H. F.: The problem of prematurity from the point of view of the obstetrician, West. J. Surg. **60**: 241-249, June, 1952.

7963. Söderhjelm, L.: Fat absorption studies in children. 1. Influence of heat treatment on milk on fat retention by premature infants, Acta paediat. **41**: 207-221, May, 1952.

7964. Cross, K. W., & Oppé, T. E.: The effect of inhalation of high and low concentrations of oxygen on the respiration of the premature infant, J. Physiol. **117**: 38-55, May, 1952.

7965. Russell, G. R., & Betts, W. A.: Natal and neonatal factors in premature infant mortality, J. Pediat. **40**: 722-732, June, 1952.

Preventive Pediatrics 7966. Batten, L. W.: Discussion on profit and loss in prophylaxis, Proc. Roy. Soc. Med. **45**: 384-388, June, 1952.

Psychiatry 7967. Zuger, B.: Growth of the individual's concept of self. Theory and some pediatric consideratons, Am. J. Dis. Child. **83**: 719-732, June, 1952.

7968. Sutter, J. M.: Conséquences éloignées des émotions de guerre chez les enfants, Pédiatrie **41**: 345-358, No. 3, 1952.
See No. 7983.

Pterygium Colli 7969. Crocozza, G.: Su diun caso di status Bonnevie-Ullrich bilateralis, Pediatria **60**: 200-215, No. 3-4, 1952.

Purpura 7970. Brust, N. M.: Ileo-ileal intussusception associated with Henoch-Schönlein's purpura, Arch. Pediat. **69**: 212-218, May, 1952.

7971. Schwartz, S. O.: Is marrow eosinophilia a valid yardstick for splenectomy in thrombocytopenic purpura? Illinois M. J. **101**: 309-311, June, 1952.

7972. Fisher, O. D., & Kraszewski, T. M.: Thrombocytopenic purpura following measles, Arch. Dis. Childhood **27**: 144-146, April, 1952.

7973. Derham, R. J., & Rogerson, M. M.: The Schönlein-Henoch syndrome and collagen disease, Arch. Dis. Childhood **27**: 139-143, April, 1952.

7974. Stefanini, M., et al.: Corticotropin (ACTH) and cortisone in idiopathic thrombocytopenic purpura, J. A. M. A. **149**: 647-653, June 14, 1952.

Pyloric Stenosis 7975. Henderson, J. L., et al.: Clinical observations on pyloric stenosis in premature infants, Arch. Dis. Childhood **27**: 173-178, April, 1952.

7976. Perrot, A., & Chanal, G.: Stènose hypertrophique du pylore, Rev. méd. Suisse Rom. **72**: 268-279, May, 1952.

Red Cell Clumping 7977. Arajärvi, T., & Zilliacus, H.: Intravascular red cell aggregation in newborn infants with infections, Acta paediat. **41**: 260-266, May, 1952.

7978. Zilliacus, H., & Aräjarvi, T.: Intravascular red cell aggregation in erythroblastosis foetalis, Acta paediat. **41**: 267-275, May, 1952.

Respiratory Tract 7979. Chapman, S. B.: Radiologic diagnosis of respiratory lesions in children, Radiology **58**: 705-710, May, 1952.

Retrolental Fibroplasia 7980. Brown, C. A., & Corner, B.: Retrolental fibroplasia. Early development and the effect of ACTH in treatment, Brit. J. Ophth. **36**: 281-302, June, 1952.

Rheumatic Diseases 7981. Richmond, J. B., & Lendrum, B. L.: Articular disorders in childhood, Illinois M. J. **101**: 295-298, June, 1952.

7982. Logue, R. B., & Hurst, J. W.: Rheumatic fever during the first few years of life and its differentiation from endocardial fibrosis, Am. J. M. Sc. **223**: 648-656, June, 1952.

7983. Bauer, I. L.: Attitudes of children with rheumatic fever, J. Pediat. **40**: 796-806, June, 1952.

Rib, Slipping 7984. Arthurton, M.: Slipping rib in a newborn child, Lancet **1**: 1142-1143, June 7, 1952.

Ringworm, Scalp 7985. Hare, P. J.: A strain of Microsporum audouini producing numerous macroconidia on culture, Brit. J. Dermat. **64**: 236-242, June, 1952.

7986. Vilanova, X., & Casanovas, M.: A study of a new species of the genus microsporum, Brit. J. Dermat. **64**: 231-235, June, 1952.

Rocky Mountain Spotted Fever 7987. Workman, J. B., et al.: Cortisone as an adjunct to chloramphenicol in the treatment of Rocky Mountain spotted fever, New England J. Med. **246**: 962-966, June 19, 1952.

Rubella 7988. Töndury, G.: Zur Wirkung des Erregers der Rubeolen auf den menschlichen Keimling, Helvet. paediat. acta **7**: 105-135, April, 1952.

Schilder's Disease. See No. 7815.

School Health 7989. Singer-Brooks, C.: Of what value are health inventories filled out by parents? Am. J. Pub. Health **42**: 661-664, June, 1952.

7990. Yankauer, A.: Designs for evaluation needed in the school health services field, Am. J. Pub. Health **42**: 655-660, June, 1952.

7991. Wilson, C. S.: School health services in England and the United States —a comparison, Am. J. Pub. Health **42**: 649-654, June, 1952.

Septicemia, Paracolon 7992. Kernohan, R. J.: Paracolon bacillus septicaemia, Lancet **1**: 1090-1091, May 31, 1952.

Septicema, Staphylococcal 7993. Wallace, E. J. G., & Jones, O. G.: Fatal staphylococcal septicaemia following removal of tonsils and adenoids, Brit. M. J. **1**: 1231, June 7, 1952.

Sinus Thrombophlebitis 7994. Symposium—Otitis media and bacteremia possibly due to sinus thrombophlebitis, J. Pediat. **40**: 792-795, June, 1952.

Speech 7995. ASHA committee on the Mid-century White House Conference—Speech disorders and speech correction, J. Speech & Hearing Disorders **17**: 129-137, June, 1952.

7996. Wischner, G. J.: An experimental approach to expectancy and anxiety in stuttering behavior, J. Speech & Hearing Disorders, **17**: 139-154, June, 1952.

7997. Moncur, J. P.: Parental domination in stuttering, J. Speech & Hearing Disorders **17**: 155-165, June, 1952.

Streptococcal Infection 7998. Bengtsson, E., & Birke, G.: Complications in penicillin-treated acute throat infections caused by B-haemolytic streptococci and among carriers of haemolytic streptococci, Acta med. scandinav. **143**: 120-128, No. 2, 1952.

Streptomycin. See No. 7801, 7903, 8020.

Stridor 7999. Symposium—Discussion on stridor in infants, Proc. Roy. Soc. Med. **45**: 355-362, June, 1952.

8000. Nabarro, S.: Calcification of the laryngeal and tracheal cartilages associated with congenital stridor in an infant, Arch. Dis. Childhood **27**: 185-186, April, 1952.

Subdural Effusion. 8001. Arnold, G. G.: The nature of postmeningitic subdural effusions, J. Pediat. **40**: 757-760, June, 1952.

Subdural Hematoma. See Hematoma, subdural.

Syphilis 8002. Bingold, A. C.: Coexistence of polyostotic fibrous dysplasia and juvenile tabes, Brit. J. Surg. **39**: 472-476, March, 1952.

8003. Euzière, J., et al: Tabo-paralysie générale juvénile, Pédiatrie **41**: 299-314, No. 3, 1952.

8004. Pigeaud, H., & Fournie, G.: Les signes objectifs de syphilis congénitale recueillis a l'autopsie de 200 nouveaunés, Semaine hôp. Paris **28**: 1642-1645, May 26, 1952.

Teaching 8005. Wangensteen, O. H.: The role of research in the modern voluntary teaching hospital, New England J. Med. **246**: 951-957, June 19, 1952.

Teeth 8006. Adler, P., & Gödény, E.: Studies on the eruption of permanent teeth. 2. The sequence of eruption, Acta genetica et statistica medica **3**: 30-49, No. 1, 1952.

8007. Wynne-Griffith, G.: The case for fluoridation, Pub. Health **55**: 142-145, June, 1952.

Terramycin. See No. 7720.

Tetanus 8008. Segar, W. E., et al: The treatment of tetanus, J. Pediat. **40**: 772-776, June, 1952.

8009. Tudor, R. B.: Tetanus resulting from foreign body in the nose, J. A. M. A. **149**: 660, June 14, 1952.

8010. Holzman, E.: Tetanus treated with chloral hydrate and myanesin, California Med. **76**: 406-407, June, 1952.

Thrombopathy 8011. Gouttas, A., et al: Deux cas de thrombopathies type Willebrand-Jurgens, Sang **23**: 328-335, No. 4, 1952.

Thymus 8012. Sarma, A. V. S.: The diagnosis of enlarged thymus in children, Antiseptic **49**: 377-378, May, 1952.

8013. Soffer, L. J., et al: Effect of **ACTH** on thymic masses, J. Clin. Endocrinol. **12**: 690-696, June, 1952.

Thyroid Hypofunction 8014. Reilly, W. A., & Bayer, D. I.: The value of the measurements of thyroid uptake and urinary excretion of I^{131} in assessing thyroid function of normal and congenitally hypothyroid children, J. Pediat. **40**: 714-721, June, 1952.

Tibia, Angulation of 8015. Bound, J. P., et al.: Congenital anterior angulation of the tibia, Arch. Dis. Childhood **27**: 179-184, April, 1952.

Tibia, Vara 8016. Langenskiöld, A.: Tibia vara. (Osteochondrosis deformans tibiae.) Acta chir. scandinav. **103**: 1-22, No. 1, 1952.

Tinea Capitis 8017. Walby, A. L.: Tinea capitis (M. audouini) in a residential school, Brit. M. J. **1**: 1114-1115, May 24, 1952.

See Ringworm.

Tonsils. See No. 7993.

Toxoplasmosis 8018. Jacobs, A. A.: Congenital ocular toxoplasmosis, New York State J. Med. **52**: 1322-1323, May 15, 1952.

Treacher Collins Syndrome. See Dysostosis mandibulofacialis.

Trichiniasis. See No. 7797.

Tuberculin Tests 8019. Cavallotti, A. M., & Gambacorti, V. G.: Esaltazione della reazione tubercolinica alla vollmer con l'aggiunta di alcune vitamine, Pediatria **60**: 160-167, No. 3-4, 1952.

Tuberculosis 8020. Wilking, V. N., et al: The occurrence of tubercle bacilli resistant to streptomycin in children with tuberculosis, Am. Rev. Tuberc. **66**: 63-76, July, 1952.

8021. Horley, J. F.: Congenital tuberculosis, Arch. Dis. Childhood **27**: 167-172, April, 1952.

Tuberculosis, Bone 8022. Fouquet, J. et al.: Sur les tuberculoses ostéo-articulaires survenant au decours des milaires traitées par la streptomycine, Rev. tuberc. **16**: 348-354, No. 4-5, 1952.

Tuberous Sclerosis 8023. Heyman, A.: Tuberous sclerosis, J. Newark Beth Israel Hosp. **3**: 192-209, July, 1952.

Tumors 8024. Andersen, D. H.: Tumors of infancy and childhood, Bull. New York Acad. Med. **28**: 480-481, July, 1952.

8025. Murano, G.: Rilievi e considerazioni su alcuni casi di tumori osservati in bambini ricoverati negli ultimi quindici anni nella Clinica Pediatrica di Napoli, Pediatria **60**: 113-136, No. 3-4, 1952.

Tumors, Adrenal 8026. Todd, R. McL.: Sudden death caused by tumour embolus in a child of four years following operative removal of suprarenal carcinoma, Brit. J. Surg. **39**: 447-452, March, 1952.

8027. Anderson, O. W.: Neuroblastoma with skeletal metastases and apparent recovery, Am. J. Dis. Child. **83**: 782-787, June, 1952.

Tumors, Bladder 8028. Youngblood, V. H., et al.: Rhabdomyosarcoma of the bladder, J. Urol. **67**: 957-961, June, 1952.

Tumors, Brain 8029. Gama, C. & Maffei, W. E.: Angio-glioma cerebral, J. Internat. Coll. Surgeons **17**: 473-481, April, 1952.

8030. Symposium—congenital brain tumor in an infant one month of age, J. Pediat. **40**: 781-785, June, 1952.

8031. Smith, A. B.: Brain tumors in children, Radiology **58**: 688-695, May, 1952.

See No. 7823.

Tumors, Eye 8032. Tebbet, R. D., & Vickery, R. D.,: Osteogenic sarcoma following irradiation for retinoblastoma, Am. J. Ophth. **35**: 811-818, June, 1952.

Tumors, Kidney 8033. Benzing, W., Jr.: Wilms' tumor of infancy and childhood, Radiology **58**: 674-687, May 1952.

Tumors, Salivary Gland 8034. Funder, J. F.: Adenoma ("mixed tumor") of submaxillary salivary gland in a boy aged eleven years, Australian & New Zealand J. Surg. **21**: 316-317, May, 1952.

Tumors, Skin 8035. Choremis, C., & Kyriakides, B: Un cas d'angioendothéliosarcome chezun nourrisson de 40 jours, à évolution favorable, Helvet. paediat. acta **7**: 202-206, April, 1952.

Tumors, Spinal Cord 8036. Schwartz, H. G.: Congenital tumors of the spinal cord in infants, Ann. Surg. **136:** 183-192, July, 1952.

8037. Symposium—Congenital neuroblastoma of the spinal canal, J. Pediat. **40:** 785-788, June, 1952.

Tumors, Spleen 8038. Ferraz, M. D., et al.: Blood cyst in a wandering spleen, J. Internat. Coll. Surgeons **17:** 521-527, April, 1952.

Tumors, Stomach 8039. Large, H. L., Jr., et al.: Gastric tridermal teratoma in infancy, J. A. M. A. **149:** 824-826, June 28, 1952.

Tumors, Testis 8040. Cook, C. D., et al.: Interstitial cell tumor of the testis. Study of a 5-year-old boy with pseudoprecocious puberty, J. Clin. Endocrinol. **12:** 725-734, June, 1952.

Tumors, Thyroid 8041. Lawler, R. H., et al: Carcinoma of the thyroid in children, Illinois M. J. **101:** 322-324, June, 1952.

8042. Clin. Case No. 693—Retarded growth and masses in neck, Case Reports Child. Mem. Hosp. Chicago, Ill. **10:** 3036-3039, June, 1952.

8043. Heptinstall, R. H., & Porritt, Sir Arthur: Recurrent "nodular goitre" in children, Brit. J. Surg. **39:** 433-441, March, 1952.

Tumors, Urethra 8044. Thorsrud, G.: Tumour of the male urethra. "Myoblastoma" of the perineal portion of the urethra, Acta chir. scandinav. **103:** 61-63, No. 1, 1952.

Urachus, Patent 8045. Geist, D. C.: Patent urachus, Am. J. Surg. **84:** 118-120, July, 1952.

Ureter, Obstruction 8046. Ormond, J. K., & Osborne, R. W.: Plastic surgery of the ureter in children, J. Urol. **67:** 860-867, June, 1952.

Urethritis 8047. Hodges, C. V.: Chronic urethritis in girls, J. A. M. A. **149:** 753-756, June 21, 1952.

Vitamins. See No. 7878.

Vitamin B_{12} 8048. Chow, B. F.: The role of vitamin B_{12} in metabolism, South. M. J. **45:** 604-612, July, 1952.

Vitamin B. Deficiency 8049. Porcelli, T.: L'ariboflavinos: del lattante, Pediatria **60:** 189-199, No. 3-4, 1952.

Waterhouse-Friderichsen Syndrome 8050. Breen, G. E., et al.: Waterhouse-Friderichsen syndrome treated with cortisone, Lancet **1:** 1140-1142, June 7, 1952.

Xanthoma 8051. Miescher, G.: Posteruptive Xanthome nach Varizellen, Dermatologica **104:** 316, No. 4-5, 1952.

Xanthomatosis 8052. Freud, P.: The relationship of xanthoma juvenile to systemic reticuloendotheliosis, J. Mt. Sinai Hosp. **19:** 243-248, May-June, 1952.

Current Pediatric References

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From the Department of Pediatrics, Marquette University, School of Medicine, Milwaukee, Wis.

Abdominal Pain. See No. 8241.

Acrocephalosyndactyly 8053. Martischnig, E., & Thalhammer, O.: Akrocephalosyndaktylie (Erörterung der Genese von Gesichtspunkt der Embryopathie), Helvet. paediat. acta **7**: 257-271, June, 1952.

ACTH 8054. Hallman, N., & Tähkä, H.: Eosinophil response to adrenalin and ACTH in severe infantile gastroenteritis and in infantile dystrophy, Ann. med. int. Fenniae **41**: 148-155, 1952.

8055. Tähkä, H., & Hallman, N.: Eosinophil response to adrenalin and ACTH in healthy infants, Ann. med. int. Fenniae **41**: 141-147, 1952.

8056. Hockerts, T., et al.: Ueber die Wirkung einiger therapeutischer Steroide und des ACTH auf bestimmte Kreislauffunktionen des Kindes, Ann. paediat. **179**: 29-40, July, 1952.

8057. Debré, R., et al.: L' A.C.T.H. et la cortisone en pédiatrie, Ann. méd. **53**: 337-413, 1952.

See Nos. 8099, 8201, 8261, 8299, 8340, 8345, 8389, and 8395.

Adolescence 8058. Trim, P. T., & Meredith, H. V.: Body form in homo sapiens: a study of five anthropometric ratios on white boys fifteen years of age, Growth **16**: 1-14, March, 1952.

8059. Kirkpatrick, M. E.: The mental hygiene of adolescence in the Anglo-American culture, Ment. Hyg. **36**: 394-403, July, 1952.

Adrenal 8060. Wolman, B.: The function of the adrenal glands in the newborn, Arch. Dis. Childhood **27**: 283-285, June, 1952.

Adrenal Insufficiency 8061. Ghins, P.: Hypertrophie congénitale des surrénales chez un nouveau-né sexe masculin, associée au tableau clinique de l'insuffisance en désoxycorticostérone, Acta paediat. Belg. **6**: 97-110, 1952.

8062. Roberts, M. H., & Baehren, P. F.: Adrenocortical insufficiency, J.M.A. Georgia **41**: 299-304, July, 1952.

Albinism, Partial 8063. Cooke, J. V.: Familial white skin spotting (piebaldness) ("partial albinism") with white forelock, J. Pediat. **41**: 1-12, July, 1952.

Allergy 8064. Rhodes, I. G.: Allergic causes of emotional disturbances in children, Nervous Child **9**: 369-377, 1952.

8065. Noelpp-Eschenhagen, I., & Noelpp, B.: Allergieproblem und Antihistamintherapie Heute, Schweiz. med. Wchnschr. **82**: 737-741, July 19, 1952.

Allergy, Gastrointestinal 8066. Derbes, V. J., & Little, E. J.: Gastro-intestinal allergy, Am. Pract. & Digest Treat. **3**: 555-561, July, 1952.

Aminoaciduria. See Cystinosis.

Anemia, Aplastic 8067. Crisalli, M., & Sansone, G.: Constitutional infantile panmyelopathy with multiple malformations (Fanconi anemia), Helvet. paediat. acta **7**: 299-308, June, 1952.

Anemia, Hemolytic 8068. Millichap, J. G.: Acute idiopathic haemolytic anemia, Arch. Dis Childhood **27**: 222-229, June, 1952.

8069. Battle, J. D., Jr.: Hereditary spherocytosis (congenital hemolytic jaundice) pathogenesis of the "hemolytic" crisis, Am. J. M. Sc. **224**: 82-92, July, 1952.

Anemia, Hypoplastic 8070. Demirăg, P. B.: A propos d'un cas d'anémie hypoplastique avec malformations congénitales multiples (anémie de Fanconi), Helvet. paediat. acta **7**: 296-298, June, 1952.

Anemia, Iron Deficiency 8071. Dickstein, B., et al.: Intravenous iron therapy in iron-deficiency anemia of infancy and childhood, Am. J. Dis. Child. **84**: 52-63, July, 1952.

Anemia, Mediterranean 8072. Bianco, I., et al.: Further data on genetics on microcythaemia or thalassaemia minor and Cooley's disease or thalassaemia major, Ann. Eugenics **16**: 299-315, May, 1952.

Anemia, Megaloblastic 8073. Veeneklaas, G. M. H.: Megalocytic deficiency anaemia cured by small amounts of fresh endive, Arch. Dis. Childhood **27**: 209-213, June, 1952.

8074. Amato, M.: Die neurologischen Erscheinungen der reversiblen Megaloblastenanämie im Kleinkindesalter, Helvet. paediat. acta **7**: 291-295, June, 1952.

Anemia, Prematurity. See No. 8321.

Anemia, Sickle-Cell 8075. Choremis, C., et al.: Sickle cell anemia in Greece, Schweiz. med. Wchnschr. **82:** 709-712, July 5, 1952.

Anesthesia 8076. Anderson, S. M.: The use of depressant drugs in infants and children (a series of 500 cases), Anesth. & Analg. **31:** 262-266, July-Aug., 1952.

8077. Voorhoeve, H. C.: Postoperative analgesia, Anesth. & Analg. **31:** 271-277, July-Aug., 1952.

8078. Wall, R. L.: Why pediatric anesthesia is different, North Carolina M. J. **13:** 343-345, July, 1952.

Anomalies, Bladder 8079. Sweetser, T. H., et al.: Exstrophy of the urinary bladder, Minnesota Med. **35:** 654-657, July, 1952.

Anomalies, Brain 8080. Vogel, F. S., & McClenahan, J. L.: Anomalies of major cerebral arteries associated with congenital malformations of the brain, Am. J. Path. **28:** 701-724, July-Aug., 1952.

8081. Zellweger, H., et al.: Zur Pathologie des Septum pellucidum im Pneumoencephalogram (PEG), Helvet. paediat. acta **7:** 229-252, June, 1952.

8082. von Muralt, G.: Cavum septi pellucidi mit operativer Bestätigung, Helvet. paediat. acta **7:** 253-256, June, 1952.

Anomalies, Diaphragm 8083. Laffont, A., & Assus, A.: A propos de deux observations d'aplasie diaphragmatique congénitale, Gynéc. et obst. **4:** 342-343, 1952.

Anomalies, Hand 8084. White, J. W., & Jensen, W. E.: The infant's persistent thumb-clutched hand, J. Bone & Joint Surg. **34A:** 680-688, July, 1952.

Anomalies, Kidney 8085. Longo, V. J., & Thompson, G. J.: Congenital solitary kidney, J. Urol. **68:** 63-68, July, 1952.

8086. Greene, L. F., et al.: Urologic abnormalities associated with congenital absence or deficiency of abdominal musculature, J. Urol. **68:** 217-229, July, 1952.

8087. Laughlin, V. C., et al.: Incomplete frontal septum of bladder complicated by congenital urethral valves and complete reduplication of upper left urinary tract, J. Urol. **68:** 289-296, July, 1952.

Anomalies, Nervous System 8088. Martin, J.: Surgical care of the neurologically defective infant, Pediatrics **10:** 150-160, July, 1952.

Anomalies, Tibia 8089. Ferguson, A. D., & Scott, R. B.: Congenital absence of the tibia, Am. J. Dis. Child. **84:** 84-89, July, 1952.

Anorexia 8090. Tolstrup, K.: Psychogenic anorexia and hyperorexia among siblings, Acta paediat. **41:** 360-372, July, 1952.

Anoxia 8091. Courville, C. B.: Ultimate residual lesions of antenatal and neonatal asphyxia, Am. J. Dis. Child. **84:** 64-78, July, 1952.

8092. Minkowski, A., et al.: L'anoxie des enfants nés après terme, Presse méd. **60:** 1005-1006, July 5, 1952.

Antibiotics 8093. Thomson, E.: The dangers of antibiotics, M. J. Australia **1:** 870-874, June 28, 1952.

8094. Kligman, A. M.: Are fungus infections increasing as a result of antibiotic therapy? J. A. M. A. **149:** 979-983, July 12, 1952.

Aorta, Aneurysm 8095. Javett, S. N., & Kahn, E.: Rupture of a mycotic aneurysm of the thoracic aorta, Arch. Dis. Childhood **27:** 294-296, June, 1952.

Appendicitis 8096. Kiss, P., et al.: Behandlung der perforierenden Appendicitis und sekundären Peritonitis im Kindesalter, Ann. paediat. **179:** 12-28, July, 1952.

Arthrogryposis Multiplex 8097. Caussade, L., et al.: Arthrogryposis multiplex. A propos de six observations, Pédiatrie **41:** 479-493, 1952.

Ascites 8098. Davidson, M. J.: Strangulated umbilical hernia and chyloperitoneum in a child with nephrosis: case report, Ann. West. Med. & Surg. **6:** 500-501, Aug., 1952.

Asthma 8099. Arbesman, C. E., et al.: Intravenous ACTH and oral cortisone in the treatment of bronchial asthma, J. Allergy **23:** 293-302, July, 1952.

Atelectasis 8100. Gans, B.: Bronchoscopic treatment of atelectasis in children, Arch. Dis. Childhood **27:** 254-256, June, 1952.

Aureomycin. See No. 8301.

Bile Duct, Cystic Dilatation 8101. Newson, A. L.: Congenital cystic dilatation of the common bile duct, M. J. Australia **1:** 784-785, June 7, 1952.

Bladder, Neurogenic 8102. James, T.: Incontinence of urine and the neurogenic bladder in childhood, Arch. Pediat. **69:** 253-265, June, 1952.

Blood, Copper in 8103. Stransky, E., et al.: On serum copper level and its importance in childhood, Ann. paediat. **179:** 1-11, July, 1952.

Blood, Zinc in 8104. Berfenstam, R.: Studies on blood zinc, Acta paediat. **41:** 7-97, May, 1952—Supp. 87.

Blood Count 8105. Leichsenring, J. M., et al.: Hemoglobin, red cell count, and mean corpuscular hemoglobin of healthy infants, Am. J. Dis. Child. **84:** 27-34, July, 1952.

Blood Formation 8106. Gairdner, D., et al.: Blood formation in infancy. 2. Normal erythropoiesis, Arch. Dis. Childhood **27**: 214-221, June, 1952.

Blood Groups 8107. Watkins, W. M.: The O and H blood group characters in the newborn, Brit. J. Exper. Path. **33**: 244-257, June, 1952.

Breast Feeding 8108. Asher, P.: The incidence and significance of breast feeding in infants admitted to hospital, Arch. Dis. Childhood **27**: 270-272, June, 1952.

Bronchiectasis 8109. Mendez, F. L., Jr., et al.: Some aspects of bronchiectasis in infants, J. Thoracic Surg. **24**: 50-57, July, 1952.

Bronchography 8110. Wishart, D. E. S.: Bronchography in children, Ann. Otol. Rhin. & Laryng. **61**: 505-514, June, 1952.

Bronchoscopy 8111. Miller, J. B., et al.: A new bronchographic technique employing aerosol anesthesia, Am. J. Roentgenol. **68**: 229-239, Aug., 1952.
See No. 8100.

Carbonic Anhydrase 8112. Berfenstam, R.: Carbonic anhydrase activity in fetal organs, Acta paediat. **41**: 310-315, July, 1952.
See No. 8317.

Cat-scratch Fever 8113. Cox, P. J. N.: Cat-scratch fever, Proc. Roy. Soc. Med. **45**: 456, July, 1952.

8114. Fox, R. A.: So-called "cat-scratch fever," Arch. Path. **54**: 75-83, July, 1952.

Celiac Disease 8115. Calabro, J. J.: Celiac disease, Clin. Proc. Child. Hosp. Wash., D. C. **8**: 154-165, July, 1952.

Cerebellar Hemorrhage. See No. 8222.

Cerebral Abscess. See No. 8220.

Cerebral Palsy 8116. Deaver, G. G.: Etiological factors in cerebral palsy, Bull. New York Acad. Med. **28**: 532-536, Aug., 1952.

Cerebral Sclerosis 8117. Corboz, J. R.: Beitrag zur Kenntnis der diffusen Hirnsklerosen, Ztschr. kinderpsychiat. **19**: 127-133, June, 1952.

Chest, Shape of 8118. Wallis, H. R. E.: Methods of recording the shape of the chest, Brit. J. Tuberc. **46**: 136-140, July, 1952.

Chloromycetin 8119. Dameshek, Wm.: Chloramphenicol (Chloromycetin) and the bone marrow, Blood **7**: 755-756, July, 1952.
See Nos. 8154 and 8389.

Chondrodystrophy 8120. Jackson, W. P. U., & Jeppe, C. L. B.: Chondrodystrophy and mental defect. Probably atypical gargoylism, South African M. J. **26**: 541-543, July 5, 1952.

Cirrhosis, Biliary. See No. 8397.

Cirrhosis, Liver 8121. Sarma, A. V. S.: Cirrhosis of the liver, Antiseptic **49**: 448-460, June, 1952.
See No. 8175.

Cobalt 8122. Virdis, S.: Azione sull'emopoiesi dei sali di cobalto, Pediatria **60**: 302-309, May-June, 1952.

Coccidioidomycosis 8123. Cohen, R., et al.: Coexisting coccidioidomycosis and tuberculosis in children, Arch. Pediat. **69**: 267-272, June, 1952.

Colic 8124. Grulee, C. G., Jr.: Colic in infancy, Mississippi Doctor **30**: 64-68, July, 1952.

Colitis, Ulcerative 8125. Beranbaum, S. L., & Waldron, R. J.: Chronic ulcerative colitis, Pediatrics **9**: 773-778, June, 1952.

Coronary Artery Disease 8126. Mant, A. K., et al.: Disease of the coronary arteries as a cause of death in infancy and childhood, Guy's Hosp. Rep. **101**: 115-125, 1952.

Cortical Hyperostosis 8127. Curtin, M.: Infantile cortical hyperostosis, Irish J. M. Sc., No. 319: 329-331, July, 1952.

Cortisone 8128. Steinberg, H., et al.: Hepatomegaly with fatty infiltration secondary to cortisone therapy: case report, Gastroenterology **21**: 304-309, June, 1952.
See Nos. 8057, 8099, 8178, 8261, 8299, 8340, 8344, and 8345.

Cough, Chronic 8129. Williams, H.: Chronic or recurrent cough in children, New Zealand M. J. **51**: 10-23, Feb., 1952.

Coxsackie Virus 8130. Kenyon, H., et al.: An outbreak of febrile illness associated with a Coxsackie virus, Lancet **2**: 153-157, July 26, 1952.

8131. Kilbourne, E. D.: The Coxsackie viruses and human disease, Am. J. M. Sc. **224**: 93-102, July, 1952.

Cryptorchidism 8132. Deming, C. L.: The evaluation of hormonal therapy in cryptorchidism, J. Urol. **68**: 354-357, July, 1952.

8133. Kiefer, J. H.: Surgical treatment of cryptorchidism, J. Urol. **68**: 358-366, July, 1952.

Cutis Laxa 8134. Wiedemann, H-R.: Einiges zum Syndrom von Ehlers und Danlos, Monatsschr. Kinderh. **100**: 252-256, May, 1952.

Cyclic Diseases. See No. 8300.

Cyst, Bone 8135. Beller, M. L.: Solitary bone cyst in the humeral mid-shaft at age five years, Bull. Hosp. Joint Dis. **13**: 212-216, April, 1952.

Cysts, Mesenteric 8136. Crouch, A. McR., Jr., & Farthing, J. W.: Mesenteric cysts, North Carolina M. J. **13**: 332-335, July, 1952.

Cystinosis 8137. Dimson, S. B.: Fanconi syndrome in two siblings, Proc. Roy. Soc. Med. **45:** 454-455, July, 1952.

8138. Weyers, H.: Neue Befunde zur Diagnose und Klinik der chronischen Aminoacidurie mit Cystinspeicherung, Acta paediat. **41:** 334-354, July, 1952.

Deafness 8139. Curry, E. T.: Analysis of hearing loss patterns in a rural Illinois school system, Ann. Otol. Rhin. & Laryng. **61:** 389-394, June, 1952.

Death, Sudden 8140. Editorial: Sudden death in infancy, Lancet **1:** 1291-1292, June 28, 1952.

Dehydration 8141. Lelong, M., et al.: Densité sanguine, pression osmotique efficace et électrocardiogramme dans la déshydratation aigue du nourrisson et sa correction, Arch. franç. pédiat. **9:** 578-600, No. 6, 1952.

Dermatitis, Follicular 8142. Bowers, R. E.: An epidemic follicular eruption, Proc. Roy. Soc. Med. **45:** 459-461, July, 1952.

Diabetes 8143. Kritzer, M. D.: The significance of the birth of a large baby, M. Clin. North America, pp. 1151-1155, July, 1952.

8144. Danowski, T. S.: Protein-bound iodine levels in normal and in diabetic children, Am. J. Dis. Child. **84:** 5-10, July, 1952.

Diagnosis, Intuitive 8145. Dreyfus, J. R.: Die dringliche Intuitivdiagnostik im Kindesalter, Schweiz. med. Wchnschr. **82:** 748-750, July 19, 1952.

Diaphragm, Radiology 8146. Swoboda, W., et al.: Conntribution à la radiologie du diaphragme chez l'enfant, Acta paediat. belg. **6:** 117-124, 1952.

Diarrheal Diseases 8147. Tolentino, P.: The importance of staphylococci in infantile parenteral gastro-enteritis, Arch. Dis. Childhood **27:** 262-264, June, 1952.

8148. Hallman, N., et al.: Electrophoretic studies of plasma proteins in severe infantile gastroenteritis, Scandinav. J. Clin. & Lab. Invest. **4:** 89-97, No. 2, 1952.

8149. Shanks, R. A., & Studzinski, L. P.: Bact. coli in infantile diarrhoea, Brit. M. J. **2:** 119-123, July 19, 1952.

8150. Krepler, P., & Zischka, W.: Role etiologique du bactérium coli IIIB4 dans les entérites du nourrisson, Pédiatrie **41:** 465-476, 1952.

See Nos. 8054 and 8292.

Diphtheria 8151. Riley, H. D., & Weaver, T. S.: Cardiovascular and nervous system complications of diphtheria, Am. Pract. & Digest Treat. **3:** 536-543, July, 1952.

Diverticulosis 8152. Gamboa, A. S., et al.: Diverticulosis del colon en la infancia, Semana méd. **100:** 843-845, June 26, 1952.

Duodenal Obstruction 8153. Shapiro, D. J., et al.: Obstruction of duodenum in the newborn infant due to annular pancreas, Pediatrics **9:** 764-772, June, 1952.

See No. 8274.

Dysentery 8154. McFadzean, A. J. S., & Stewart, P. D.: Chloramphenicol in acute Shigella dysentery, Lancet **2:** 166-168, July 26, 1952.

Dysostosis, Cleidocranial 8155. Herndon, C. N.: Cleidocranial dysostosis, Am. J. Human Genet. **3:** 314-324, Dec., 1951.

Dysostosis, Multiplex 8156. Rodeck, H., et al.: Klinische und klinisch-chemische Untersuchungen bei Dysostosis multiplex (Morbus Pfaundler-Hurler), Arch. Kinderh. **144:** 251-259, 1952.

Dysplasia, Epiphysialis Multiplex 8157. Scott, L. G.: Dysplasia epiphysialis multiplex, Proc. Roy. Soc. Med. **45:** 452, July, 1952.

Dysplasia, Epiphysialis Punctata 8158. Scott, L. G.: Dysplasia epiphysialis punctata, Proc. Roy. Soc. Med. **45:** 453, July, 1952.

Dystonia Musculorum 8159. Corner, B. D.: Dystonia musculorum deformans in siblings. Treated with Artane (trihexylphenidyl), Proc. Roy. Soc. Med. **45:** 451-452, July, 1952.

Eczema 8160. Woringer, P.: Le traitement de l'eczéma du nourrisson par le salicylate de soude: note préliminaire, Arch. franç. pédiat. **9:** 630-632, 1952.

Electrocardiography 8161. Taran, L. M., & Szilagyi, N.: Technical considerations in the measurement of the electrical systole (QT interval) and its relationship to the electrical events in the cardiac cycle, Bull. St. Francis San. **9:** 15-37, July, 1952.

8162. Schaffer, A. I., & Beinfield, W. H.: The vectorcardiogram of the newborn infant, Am. Heart J. **44:** 89-94, July, 1952.

Electroencephalography 8163. Chaptal, J., et al.: Les traces de monorythmie sinusoidale lente a inscription postérieure, et de méningo corticalite, Montpellier Médical **41/42:** 194-220, Mar./Apr., 1952.

8164. Feldmann, H.: L'électro-encéphalogramme dans les troubles du caractère et du comportement chez l'enfant, Schweiz., Arch. Neurol. u. psychiat. **69:** 170-212, 1-2, 1952.

Electrolytes 8165. Shukers, C. F.: Review of estimation of serum sodium and potassium, Am. J. Clin. Path. **22:** 606-615, July, 1952.

8166. Cooper, I. S., & Crevier, P. H.: Neurogenic hypernatremia and hyperchloremia, J. Clin. Endocrinol. **12:** 821-830, July, 1952.

Emotional Disturbances. See No. 8064.

Encephalitis, Measles 8167. Jennings, G. H.: Loss and recovery of sight in measles encephalitis, Lancet **2**: 66-67, July 12, 1952.

Encephalitis Periaxialis, Diffusa. See No. 8117.

Encephalitis, Postvaccinal 8168. Jongco, A. P., & Felix, N. S.: Post-vaccination encephalitis, Acta med. philippina **8**: 87-93, 1951.

8169. Mulè, F.: Su di un caso di encefalomielopatia durante le reazione vaccino-vaiolosa, Pediatria **60**: 330-338, May-June, 1952.

Endocardial Fibroelastosis 8170. Tricot, R., et al.: Étude clinique et hémodynamique de la persistance du canal artériel, Semaine hôp. Paris **28**: 2150-2154, July 6, 1952.

Eosinophils. See Nos. 8054 and 8055.

Epilepsy 8171. Pond, D. A.: Psychiatric aspects of epilepsy in children, J. Ment. Sc. **98**: 404-410, July, 1952.

8172. Robb, P., & McNaughton, F.: Etiology and medical management of epilepsy in children, Pediatrics **9**: 788-790, June, 1952.

Epilepsy, Postencephalitis 8173. Rett, A.: Ueber Eosinophilie und vegetative Regulations-störungen bei einem Fall von postencephalitischer Epilepsie, Helvet. paediat. acta **7**: 281-290, June, 1952.

Erythroblastosis, Fetal 8174. Gesteira, M.: Ictericias do recém nascido e eritroblastose fetal. Problemas de etiopatogenia e diagnose, Arch. pediat. Uruguay **23**: 279-298, May, 1952.

8175. Gerrard, J.: Icterus gravis and cirrhosis of the liver, Brit. M. J. **1**: 1385-1387, June 28, 1952.

8176. MacRae, D. J.: Green teeth in baby due to rhesus incompatability, Proc. Roy. Soc. Med. **45**: 439, July, 1952.

8177. Wiener, A. S., & Brancato, G. J.: Problems in the management of erythroblastosis fetalis, with five examples exhibiting unusual serological findings, J. Lab. & Clin. Med. **40**: 27-38, July, 1952.

8178. Hunter, O. B., Jr., & Ross, J. B.: Cortisone in Rh incompatabilities, South. M. J. **45**: 732-738, Aug., 1952.

8179. Matson, G. A., & Koucky, R. W.: Blood group factors. Part 2. Rh sensitization, Minnesota Med. **35**: 641-649, July, 1952.

8180. Patzer, H.: Kernikterus und Capillarpermeabilität, Monatsschr. Kinderh. **100**: 263-267, May, 1952.

Erythroderma desquamativa 8181. Ivády, J., & Buzás, G.: Le contenu en hormone antidurétique du liquide céphalorachidien des nourrissons atteints de maladie de Leiner, Ann. pediat. **179**: 41-49, July, 1952.

Esophagus, Atresia 8182. Wilton, T. N. P.: Anaesthesia for oesophageal surgery in infants and children, Anesth. & Analg. **31**: 267-270, July-Aug., 1952.

8183. Johnson, E. K., & Mangiardi, J. L.: Atresia of cervical esophagus, J. Thoracic Surg. **24**: 75-79, July, 1952.

Fat Absorption 8184. Söderhjelm, L.: Fat absorption studies in children. 2. Influence of propylene glycol, lecithin, choline, aureomycin, and low fat diet on fat retention in children, Acta paediat. **41**: 316-324, July, 1952.

8185. Söderhjelm, L.: Fat absorption studies in children. 3. Fat tolerance tests, Acta paediat. **41**: 325-333, July, 1952.

Feeding 8186. Vining, C. W.: Feeding disorders in infants; their interpretation, Lancet **2**: 99-101, July 19, 1952.

8187. Barnes, D. J.: Feeding normal children, Harper Hosp. Bull. **10**: 86-93, May-June, 1952.

8188. Rabinovitch, R. D., & Fischhoff, J.: Feeding children to meet their emotional needs, J. Am. Dietet. A. **28**: 614-621, July, 1952.

8189. Kunz, H. W.: Paraffin-tipped polyethylene tubing for feeding of premature babies, infants, and children, J. Pediat. **41**: 84-85, July, 1952.

8190. Müller, E.: Ueber Wesen und Aufgaben unausnutzbarer Polysaccharide in der künstlichen Säuglingsernährung, Ztschr. Kinderh. **71**: 120-135, 1952.

See No. 8376.

Feeding, Tube Method in. See No. 8316.

Galactosemia 8191. Edmonds, A. M., et al.: Galactosemia, Pediatrics **10**: 40-47, July, 1952.

Gamma Globulin Deficiency 8192. Bruton, O. C.: Agammaglobulinemia, Pediatrics **9**: 722-728, June, 1952.

Gangrene, Newborn 8193. Symposium: Gangrene of the newborn, Gynéc. et obst. **4**: 361-364, 1952.

Gargoylism 8194. Henderson, J. L., et al.: The pathology and biochemistry of garboylism, Arch. Dis. Childhood **27**: 230-253, June, 1952.

Gastritis, Emphysematous 8195. Henry, G. W.: Emphysematous gastritis, Am. J. Roentgenol. **68**: 15-18, July, 1952.

Gastroenteritis. See Diarrheal Diseases.

Gaucher's Disease 8196. Habermann, P.: Pseudomiliares Lungenbild bei Morbus Gaucher, Arch. Kinderh. **144:** 268-272, 1952.

Glutamic Acid 8197. Foale, M.: The treatment of mental defectives with glutamic acid, J. Ment. Sc. **98:** 483-487, July, 1952.

8198. Harbauer, H., & De Boor, W.: Erfahrungen mit Glutaminsäure an Schwachbegabten, Monatsschr. Kinderh. **100:** 281-283, June, 1952.

8199. Göllnitz, G.: Behandlungsresultate mit Glutaminsäure an Kindern mit exogenem und endogenem Schwachsinn, Monatsschr. Kinderh. **100:** 277-280, June, 1952.

8200. Schwöbel, G.: Untersuchungen über die Wirkung der L+ Glutaminsäure auf intellektuelle und gemütliche Funktionen bei debilen und imbezillen Kindern, Ztschr. Kinderpsychiat. **19:** 101-126, June, 1952.

Glycogen Storage Disease 8201. Ulstrom, R. A., et al.: Metabolic and clinical effects of corticotropin (ACTH) on essential glycogenosis (von Gierke's disease), Metabolism **1:** 291-299, July, 1952.

Growth 8202. Bryan, A. H., & Greenberg, B. G.: Methodology in the study of physical measurements of school children, Human Biol. **24:** 117-143, May, 1952.

8203. Yudkin, J.: Effect of liver supplement on growth of children, Brit. M. J. **1:** 1388-1389, June 28, 1952.

8204. Scholten, C.: Die konstitutionelle Entwicklungshemmung im Kindes- und Jugendalter als diagnostisches und therapeutisches Problem, Med. Klin. **47:** 898-901, July 4, 1952.

8205. Freund, J., & Maier, E-H.: Zur Aetiologie der Entwicklungsbeschleunigung, Ztschr. Kinderh. **71:** 79-104, 1952.

See No. 8339.

Hayfever 8206. Ratner, B.: Treatment of hay fever in children, GP **6:** 47-50, July, 1952.

Heart. See No. 8284.

Heart Disease, Congenital 8207. Orme, H. W., & Adams, F. H.: The relationship of intracardiac pressures and electrocardiographic findings in cases of congenital heart disease, J. Pediat. **41:** 53-72, July, 1952.

8208. Routier, D.: L'Électrocardiogramme dans les malformations congénitales cardiaques, Semaine hôp. Paris **28:** 2130-2135, July 6, 1952.

8209. Deglaude, L., & Laurens, P.: Recherches vectographiques dans les cardiopathies congénitales, Semaine hôp. Paris **28:** 2135-2149, July 6, 1952.

8210. Goldman, I. R., & Stern, N. S.: Congenital malformation of the heart in one of identical twins, Am. Heart J. **44:** 159-163, July, 1952.

8211. Dammann, J. F., Jr.: Patent ductus arteriosus in the absence of a continuous murmur, Circulation **6:** 110-124, July, 1952.

8212. Lesser, M. B.: Coarctation of the aorta and patent ductus arteriosus, Arch. Pediat. **69:** 273-276, June, 1952.

8213. Robb, D., & Nicks, R.: The surgical treatment of patent ductus arteriosus, New Zealand M. J. **51:** 31-34, Feb., 1952.

8214. Soulie, P., et al.: Voie infundibulaire et tétrade de Fallot, Semaine hôp. Paris **28:** 2119-2127, July 6, 1952.

8215. Biörck, G., et al.: Unusual cyanosis in a boy with congenital pulmonary stenosis and tricuspid insufficiency, fatal outcome after angiocardiography, Am. Heart J. **44:** 143-148, July, 1952.

8216. Madoff, I. M., et al.: Congenital absence of the right pulmonary artery, New England J. Med. **247:** 149-157, July 31, 1952.

8217. Dunn, H. G.: Congenital partial heart block, Proc. Roy. Soc. Med. **45:** 456-458, July, 1952.

8218. Bret, J.: Indications et résultats des opérations de Blalock, de Potts et de Brock, dans 200 cas de sténose pulmonaire, Arch. mal. coeur **45:** 577-584, July, 1952.

8219. Muller, W. H., Jr., & Dammann, J. F., Jr.: The treatment of certain congenital malformations of the heart by the creation of pulmonic stenosis to reduce pulmonary hypertension and excessive pulmonary blood flow, Surg., Gynec. & Obst. **95:** 213-219, Aug., 1952.

8220. Roger, H., et al.: Les abcès cérébraux au cours des affections congénitales du coeur, Rev. Neurol. **86:** 209-222, 1952.

See No. 8275.

Hemangioma, Cerebral 8221. Werner, E.: Die Sturge-Webersche Krankheit und ihre Beziehung zu den Phakomatosen, Arch. Kinderh. **144:** 259-268, 1952.

Hematoma, Extradural 8222. Gage, E. L.: Recurrent extradural cerebellar hematoma, Am. J. Dis. Child. **84:** 82-83, July, 1952.

Hematoma, Subdural 8223. Symposium: Subdural haematoma, Lancet **2:** 135, July 19, 1952.

8224. Anderson, F. M.: Subdural hematoma, a complication of operation for hydrocephalus, Pediatrics **10:** 11-18, July, 1952.

Hemorrhagic Diseases 8225. Quick, A. J.: Abnormal bleeding in childhood, Postgrad. Med. **12:** 89-93, July, 1952.

Hepatitis 8226. Bennett, A. M., et al.: Endemic infectious hepatitis in an infants' orphanage, Arch. Int. Med. **90:** 37-53, July, 1952.

8227. Hsia, D. Y.: A long-term follow-up study on infectious hepatitis during pregnancy, J. Pediat. **41:** 13-17, July, 1952.

8228. Gipson, A. C.: Pediatric case reports, J. M. A. Alabama **22:** 19-21, July, 1952.

8229. Weisse, K.: Die Hepatitis epidemica im ersten Lebenshalbjahr, Ztschr. Kinderh. **71:** 136-153, 1952.

Hernia, Diaphragmatic 8230. Lawler, R. H., et al.: Treatment of diaphragmatic hernia in the newborn, Am. J. Dis. Child. **84:** 79-81, July, 1952.

Hernia, Umbilical 8231. Jelliffe, D. B.: The origin, fate and significance of the umbilical hernia in Nigerian children, Tr. Roy. Soc. Trop. Med. & Hyg. **46:** 428-434, July, 1952.
See No. 8098.

Hip, Arthrography 8282. Kenin, A., & Levine, J.: A technique for arthrography of the hip, Am. J. Roentgenol. **68:** 107-111, July, 1952.

Hip Dislocation, Congenital 8233. Nisbet, N. W.: Congenital dislocation of the hip, New Zealand M. J. **51:** 2-10, Feb., 1952.

8254. Kite, J. H., & King, R. E.: Early diagnosis and treatment of congenital dislocation of the hip, J. M. A. Georgia **41:** 291-295, July, 1952.

Histoplasmosis 8235. Payne, N. S., et al.: Histoplasmosis occurrence in Virginia, Virginia M. Month. **79:** 430-435, Aug., 1952.

Hodgkin's Disease 8236. Tanner, N. M.: Hodgkin's disease in childhood, J. Nat. M. A. **44:** 261-269, July, 1952.

Hospitals 8237. Lloyd, W., & Heinstein, M.: An experimental approach to mental health in program of a children's hospital, Ment. Hyg. **36:** 423-438, July, 1952.

8238. Bakwin, H.: Hospital care of the sick child, Bull. St. Francis San. **9:** 1-14, July, 1952.

8239. Steuart, G. W.: Emergency hospitalization of young children, South African M. J. **26:** 472-476, June 7, 1952.

Hyaline Membrane 8240. Lantuéjoul, P., & Héraux, A.: Note sur la "membrane hyaline," Gynéc. et obst. **4:** 208-213, 1952.

Hydrocephalus. See Nos. 8224 and 8269.

Hydronephrosis 8241. Lohrey, R. C., et al.: Stomach pain caused by masked hydronephrosis, J. A. M. A. **149:** 1212-1213, July 26, 1952.

Hygroma 8242. Stadler, H. E., et al.: Hygroma colli, J. Pediat. **41:** 100-103, July, 1952.

Hypertelorism 8243. Caussade, L., et al.: Nouvelles remarques sur l'hypertélorisme de Greig, Arch. franç. pédiat. **9:** 639-641, 1952.

Hypertension 8244. Cutforth, R. H.: Malignant hypertension in a girl of 16, Proc. Roy. Soc. Med. **45:** 442-443, July, 1952.

Hypoproteinemia 8245. Wyngaarden, J. B., et al.: Idiopathic hypoproteinemia, Pediatrics **9:** 729-735, June, 1952.

Hypospadias 8246. Dodson, A. I., & Frohbose, W. J.: Hypospadias, J. Michigan M. Soc. **51:** 852-856, July, 1952.

Immunization 8247. Pearlman, L. N.: Early immunization—its possible influence on Canadian mortality figures, Am. J. Dis. Child. **84:** 11-16, July, 1952.

Immunology 8248. Osborn, J. J., et al.: Studies of the immunology of the newborn infant, Pediatrics **9:** 736-744, June, 1952.

Inclusion Disease 8249. Linzenmeier, G.: Die Bedeutung des Speicheldrüsenvirus für den Menschen unter dem morphologischen Bild der Cytomegalie, Ztschr. Kinderh. **71:** 162-182, 1952.

Intestine, Bacteriology 8250. Itoga, G., et al.: Observations on the persistence of coliform bacteria in the intestines of infants and newborn babies: on oral administration with a specially "labelled" strain, Keio J. Med. **1:** 69-79, Jan., 1952.

Intestine, Rupture 8251. Sanford, M. C., & McLendon, P. A.: Rupture of the bowel in a newborn infant, Clin. Proc. Child. Hosp. Wash., D. C. **8:** 165-172, July, 1952.

Intussusception 8252. Ravitch, M. M.: Consideration of errors in the diagnosis of intussusception, Am. J. Dis. Child. **84:** 17-26, July, 1952.

Kartagener's Triad 8253. Torgersen, J.: The triad of Kartagener, Schweiz. med. Wchnschr. **82:** 770-771, July 26, 1952.

Kidney, Polycystic 8254. Lih, B., & Waud, R. E.: Unilateral polycystic kidney in a newborn, J. Urol. **68:** 60-62, July, 1952.

Lens, Rupture of 8255. Orlansky, G. J.: Spontaneous rupture of the lens in hydrocephalic epilepsy, Arch. Pediat. **69:** 247-252, June, 1952.

Leukemia 8256. Leikin, S., et al.: The treatment of acute leukemia in children, J. Pediat. **41:** 40-46, July, 1952.

8257. Tivey, H.: Prognosis for survival in the leukemias of childhood, Pediatrics **10**: 48-59, July, 1952.

Liver Extract. See No. 8203.

Liver, Fatty. See No. 8128.

Liver, Rupture 8258. Epstein, H. J., & Lipshutz, B.: Hemobilia, cholecystitis, and gastrointestinal bleeding with rupture of liver, J. A. M. A. **149**: 1132-1133, July 19, 1952.

Liver, Steatosis 8259. Chaptal, J., et al.: Stéatose hépatique du nourrisson, Montpellier Médical **41/42**: 91-116, Mar.-Apr., 1952

Löffler's Syndrome 8260. Grimmett, M. H., et al.: Loeffler's syndrome, North Carolina M. J. **13**: 337-340, July, 1952.

Lupus Erythematosus 8261. Dubois, E. L.: Case report: Systemic lupus erythematosus treated with ACTH and cortisone, Univ. South Calif. Med. Bull. **4**: 18-19, July, 1952.

Lymphadenitis 8262. Betke, K.: Zur Klinik und Cytodiagnostik chronischer Lymphknotenerkrankungen: die Virus-kratzlymphadenitis (benigne Inokulationslymphoretikulose), Schweiz. med. Wchnschr. **30**: 583-588, July 1, 1952.

Manic-Depressive Illness 8263. Symposium: The problem of depressive and manic sickness in childhood, Nervous Child **9**: 310-368, 1952.

Mastoiditis, Tuberculous 8264. DeReynier, J. P.: A propos d'un cas de mastoïdite tuberculeuse chez un enfant de 14 mois, Schweiz. Ztschr. Tuberk. **9**: 336-342, 1952.

Megacolon 8265. State, D.: Surgical treatment for idiopathic congenital megacolon. (Hirschsprung's disease), Surg., Gynec. & Obst. **95**: 201-212, Aug., 1952.

Meningitis, Listeria 8266. Line, F. G., & Appleton, F. G.: Listeria meningitis in a premature infant, J. Pediat. **41**: 97-99, July, 1952.

Meningitis, Lymphocytic 8267. Letman, H.: Abacterial meningitis with high protein content in the spinal fluid, Acta psychiat. et neural. **27**: 85-89, 1952.

Meningitis, Meningococcus 8268. Petit, R., & de Ripainsel, M.: A propos d'un cas de méningite double, méningococcique et tuberculeuse, Acta paediat. belg. **6**: 139-144, 1952.

Meningitis, Tuberculous 8269. Knorr, G.: Beitrag zur Morphologie des Hydrocephalus bei chronischer Leptomeningitis tuberculosa durch Streptomycin, Beitr. klin. Tuberk. **107**: 117-133, 1952.

8270. Lüchtrath, H.: Tuberkulöse meningitis und Zwischenhirn, Ztschr. Kinderh. **71**: 105-119, 1952.

See No. 8268.

Mental Deficiency. See Nos. 8197, 8198, 8199, and 8302.

Migraine 8271. Michael, M. I., & Williams, J. M.: Migraine in children, J. Pediat. **41**: 18-24, July, 1952.

8272. Jackobsen, H-H.: Unilateral sympathetic hypofunction in migraine, Acta psychiat. et neurol. **27**: 67-82, 1952.

8273. Svendsen, B. B.: Different course of migraine in monozygotic twins, Acta psychiat. et neurol. **27**: 165-174, 1952.

Mongolism 8274. Louw, J. H.: Congenital duodenal stenosis and mongolism, South African M. J. **26**: 521-522, June 28, 1952.

8275. Granata, G., et al.: Contributo alla conoscenza delle malformazioni cardiache congenite nei soggetti mongoloidi, Pediatria **60**: 281-301, May-June, 1952.

Moniliasis. See No. 8094.

Mononucleosis, Infectious 8276. Marshall, S., & Millingen, K. S.: Unusual features in a fatal case of infectious mononucleosis, Brit. M. J. **1**: 1325-1327, June 21, 1952.

Mortality, Infant 8277. Smith, A. C.: La réduction de la mortalité foetale et néonatale, Pediatrie **41**: 447-464, 1952.

Muscular Dystrophy 8278. Mock, W.: Zum Erbbild der progressiven Muskeldystrophie, Monatsschr. Kinderh. **100**: 271-273, May, 1952.

Mycotic Diseases 8279. Haley, L. D.: Mycotic diseases in pediatric practice, J. Pediat. **41**: 104-112, July, 1952.

Nail Biting 8280. Malone, A. J., & Massler, M.: Index of nailbiting in children, J. Abnorm. & Social Psychol. **47**: 193-202, April, 1952.

Neck, Webbed. See No. 8388.

Nephrosis 8281. Kagan, B. M., & Kaiser, E.: Vitamin A concentration in the liver in the nephrotic syndrome, J. Lab. & Clin. Med. **40**: 12-16, July, 1952.

Neurofibromatosis 8282. Ayres, W. W., et al.: Congenital neurofibromatous macroglossia associated in some cases with von Recklinghausen's disease, Cancer **5**: 721-726, July, 1952.

Newborn 8283. Matoth, Y.: Phagocytic and ameboid activities of the leukocytes in the newborn infant, Pediatrics **9**: 748-755, June, 1952.

8284. Hunt, W. E.: Spontaneous rupture of the heart in the newborn infant, Arch. Dis. Childhood **27**: 291-293, June, 1952.

See Nos. 8060, 8092, 8107, 8153, 8162, 8227, 8248, 8251, 8254, 8293, and 8351.

Niemann-Pick's Disease 8285. Videbaek, A.: Another case of Niemann-Pick's disease observed in Denmark, Acta paediat. **41**: 355-359, July, 1952.

Nuchal Rigidity, Familial 8286. Sutro, C. J., & Mishkin, R. D.: Familial nuchal rigidity, Bull. Hosp. Joint Dis. **13**: 155-163, April, 1952.

Oligophrenia phenylperuvica 8287. Schrappe, O.: Zur pathologischen Physiologie des Phenylbrenztraubensäure - Schwachsinns, Nervenarzt **23**: 175-180, May 20, 1952.

Orthodontia 8288. Graber, T. M.: Orthodontic problems in pediatric practice, Pediatrics **9**: 709, 721, June, 1952.

Osteomyelitis 8289. Giaccai, L., & Idriss, H.: Osteomyelitis due to salmonella infection, J. Pediat. **41**: 73-78, July, 1952.

8290. O'Brien, R. M.: Acute and chronic osteomyelitis, Postgrad. Med. **12**: 133-136, Aug., 1952.

8291. Propers, A.: Ueber Osteomyelitis im frühen Kindesalter, Arch. Kinderh. **144**: 223-236, 1952.

Otitis 8292. Biesalski, P.: Therapieprobleme der entzündlichen Mittelohr- und Nasenerkrankungen bei den akuten und chronischen Ernährungsstörungen im Säuglingsalter, Arch. Kinderh. **144**: 193-209, No. 3, 1952.

Oxygen Saturation 8293. Prec, K. J., & Cassels, D. E.: Oximeter studies in newborn infants during crying, Pediatrics **9**: 756-763, June, 1952.

Pancreas, Annular. See No. 8153.

Pancreas, Fibrocystic Disease 8294. Tomlin, C. E., et al.: Chronic cor pulmonale as a complication of fibrocystic disease of the pancreas, Am. Heart J. **44**: 42-50, July, 1952.

8295. Emery, J. L.: Variation in the proteolytic activity of children's stools, Arch. Dis. Childhood **27**: 257-261, June, 1952.

8296. Freudenberg, E.: Der Duodenalsaft bei der Pankreasfibrose, Monatsschr. Kinderh. **100**: 242-244, May, 1952.

8297. Schwachman, H., et al.: Antibiotics in treatment of pancreatic fibrosis, with emphasis on terramycin, J. A. M. A. **149**: 1101-1108, July 19, 1952.

Pediatrics 8298. Slobody, Lawrence B.: Survey of Clinical Pediatrics, ed. 1, 1952, McGraw-Hill Books, 471 pp.

Penicillin. See No. 8346.

Periarteritis 8299. Lelong, M., et al.: Deux cas de périartérite nouese traités par l'A.C.T.H. et par la cortisone, Arch. franç. pédiat. **9**: 620-627, 1952.

Periodic Disorders 8300. Franklin, A. W.: Periodic disorders of children, Lancet **1**: 1267-1270, June 28, 1952.

Pertussis 8301. Oberbauer, W.: Zur Behandlung des Keuchhustens mit Streptomycin und Aureomycin, Arch. Kinderh. **144**: 236-251, 1952.

Piebaldness. See No. 8063.

Pituitary, Hypofunction 8302. Kugelmass, I. N.: Mental deficiency of hypopituitarism in childhood, New York J. Med. **52**: 1655-1659, July 1, 1952.

Pneumomediastinum 8303. Effron, B.: Pneumomediastinum (Mediastinal emphysema) in a premature infant, J. Pediat. **41**: 94-96, July, 1952.

Pneumonia, Staphylococcic 8304. Keizer, D. P. R.: La pneumonia à staphylocoques et la radiologie, Acta paediat. belg. **6**: 125-128, 1952.

Poisoning, DDT 8305. Cunningham, R. E., & Hill, F. S.: Convulsions and deafness following ingestion of DDT, Pediatrics **9**: 745-747, June, 1952.

Poisoning, Insecticide 8306. Lensky, P., & Evans, H. L.: Human poisoning by chlordane, J. A. M. A. **149**: 1394-1395, Aug. 9, 1952.

Poisoning, Potassium-Permanganate 8307. Rudat, K-D.: Ein Fall von akuter Vergiftung mit Kaliumpermanganat, Monatsschr. Kinderh. **100**: 299-301, June, 1952.

Poliomyelitis 8308. Miller, A. H.: Incidence of poliomyelitis, California Med. **77**: 19-21, July, 1952.

8309. Drake, R. M.: Poliomyelitis and parenteral injections, California Med. **77**: 22-28, July, 1952.

8310. Bodian, D.: Experimental studies on passive immunization against poliomyelitis, Am. J. Hyg. **56**: 78-89, July, 1952.

8311. Mangold, G.: Betrachtungen zu epidemiologischen Untersuchungen über die Wiesbadener Poliomyelitis-epidemie 1950, Ztschr. Hyg. **134**: 439-461, 1952.

8312. Symposium: Diagnosis and clinical features of poliomyelitis, M. J. Australia **2**: 1-23, July 5, 1952.

8313. Mulè, F.: Il complesso vitamina K-tossina tetanica nel trattamento della poliomielite, Pediatria **60**: 261-275, May-June, 1952.

8314. Davis, H. S., & Bishop, H. F.: Airway management in patients with poliomyelitis. J. A. M. A. **149**: 1175-1180, July 26, 1952.

8315. Gear, J.: Immunity to poliomyelitis, Ann. Int. Med. **37**: 1-22, July, 1952.

Prematurity 8316. Wagner, E. A., et al.: Polyethylene tube feeding in premature infants, J. Pediat. **41**: 79-83, July, 1952.

8317. Berfenstam, R.: Studies on carbonic anhydrase activity in children. 2. Possibilities of influencing the carbonic anhydrase activity in the blood of premature infants, Acta paediat. **41**: 297-309, July, 1952.

8318. Schoeneck, F. J.: Obstetrical versus pediatric responsibility in prematurity, Am. J. Obst. & Gynec. **64:** 126-133, July, 1952.

8319. Agerty, H. A., & Seitchik, J. N.: Experimental use of methyl testosterone and testosterone in premature infants, Pediatrics **10:** 28-32, July, 1952.

8320. James, U., & Coles, B. L.: Methyl testosterone in premature infants, Arch. Dis. Childhood **27:** 265-269, June, 1952.

8321. Reedy, M. E., et al.: Anemia of the premature infant, J. Pediat. **41:** 25-39, July, 1952.

8322. Babson, S. G.: Feeding the premature, Northwest Med. **51:** 596, July, 1952.

8323. Köttgen, H. U., & Feyerabend, H.: Störungen der Reizbildung und Erregungsleitung im Herzen bei frühgeborenen Kindern, Monatsschr. Kinderh. **100:** 244-250, May, 1952.

8324. Laumonier, R.: Remarques sur la structure pulmonaire des prématurés, Semaine hôp. **28:** 2047-2053, June 30, 1952.

See Nos. 8266 and 8303.

Pseudohypoparathyroidism 8325. Bille, BO S. V.: Pseudohypoparathyroidism, Acta paediat. **41:** 380-389, July, 1952.

Psychiatry 8326. Milman, D. H.: Group therapy with parents: an approach to the rehabilitation of physically disabled children, J. Pediat. **41:** 113-116, July, 1952.

8327. Wellisch, E.: Eye manifestations in maladjusted children, J. Ment. Sc. **98:** 457-463, July, 1952.

8328. Freed, H., & Meals, D. W.: Group therapy program with children at Philadelphia General Hospital, J. Philadelphia Gen. Hosp. **3:** 127-131, July, 1952.

8329. Marcus, I. M.: Clinical aspects of childhood schizophrenia: viewed from integrative levels, New Orleans M. & S. J. **104:** 541-548, July, 1952.

8330. Villinger, W.: Moderne Probleme der Jugendpsychiatrie, Nervenarzt **23:** 201-209, June 20, 1952.

8331. Soddy, K.: Mental health and the maladjusted child, Ment. Hyg. **36:** 383-393, July, 1952.

8332. von Poten, I.: Die Verwendung des Sceno-tests zur tiefenpsychologischen Untersuchung des Kindes, Monatsschr. Kinderh. **100:** 283-292, June, 1952.

See Nos. 8064 and 8171.

Psychopathic Personality 8333. Sands, D. E., & Chamberlain, G. H. A.: Treatment of inadequate personality in juveniles by dehydroisoandrosterone, Brit. M. J. **2:** 66-68, July 12, 1952.

Ptosis, Congenital 8334. Scott, G. I.: Operative treatment of congenital ptosis, Brit. J. Ophth. **36:** 362-372, July, 1952.

Ptyalorrhea 8335. Keizer, D. P. R.: Ptyalorrhoea ejaculativa, Pediatrie **41:** 495-497, 1952.

Pyloric Stenosis 8336. Astley, R.: The radiology of infantile pyloric stenosis, Brit. J. Radiol. **25:** 342-352, July, 1952.

Retrolental Fibroplasia 8337. Locke, J. C., & Reese, A. B.: Retrolental fibroplasia, Arch. Ophth. **48:** 44-47, July, 1952.

8338. Crosse, V. M., & Evans, P. J.: Prevention of retrolental fibroplasia, Arch. Ophth. **48:** 83-87, July, 1952.

Rheumatic Diseases 8339. Kahn, L., et al.: Wetzel grid analysis of rheumatic children, J. Pediat. **41:** 47-52, July, 1952.

8340. Riley, I. D., & Speirs, A. L.: Fatal rheumatic pericarditis treated with cortisone and ACTH, Glasgow M. J. **33:** 255-256, June, 1952.

8341. Aikawa, J. K.: The cell membrane defect in acute rheumatic fever, North Carolina M. J. **13:** 330-331, July, 1952.

8342. Halonen, P. I., et al.: Some aspects of Mester's test in rheumatic diseases, Ann. med. int. Fenniae **41:** 79-86, No. 2, 1952.

8343. Burgemeister, G.: EKG und rheumatische Herzerkrankung, Monatsschr. Kinderh. **100:** 267-271, May, 1952.

8344. Josserand, P., et al.: Résultats du traitement hormonal de la maladie de bouillaud chez l'enfant, Pédiatrie **41:** 499-507, No. 4, 1952.

8345. Young, D., & Rodstein, M.: Results of cortisone-corticotropin therapy in chronic active rheumatic fever, Arch. Int. Med. **90:** 64-78, July, 1952.

8346. Gale, A. H., et al.: Oral penicillin in the prophylaxis of streptococcal infection in rheumatic children, Lancet **2:** 61-63, July 12, 1952.

8347. McCulloch, H.: Some ideas on the nature of rheumatic fever, Am. J. Dis. Child. **84:** 1-4, July, 1952.

Salivary Gland: Virus Infection. See No. 8249.

Salmonella Infection 8348. Hinden, E., et al.: An outbreak due to Salmonella brancaster, Lancet **2:** 64-66, July 12, 1952.

See No. 8289.

Scarlet Fever 8349. Ket, W. M.: Scarlet fever, M. J. Australia **1:** 850-852, June 21, 1952.

8350. Schmager, A.: Die Rachenflora bei mit penicillin behandeltem Scharlach, zugleich ein Beitrag zur Frage der generellen Therapie des Scharlachs mit Penicillin, Ztschr. Hyg. **134:** 462-473, 1952.

Scoliosis, Congenital 8351. Guyot, J. M.: Scoliose congénitale, Helvet. paediat. acta **7**: 272-280, June, 1952.

Sexual Precocity 8352. Jacobsen, W., & Macklin, M. T.: Hereditary sexual precocity, Pediatrics **9**: 682-695, June, 1952.

Sinusitis 8353. Freund, E. M.: Sinusitis in children and infants, New York J. Med. **52**: 1660-1662, July 1, 1952.

Sleep 8354. Illingworth, R. S.: Sleep problems in the first three years, J. Roy. Inst. Pub. Health & Hyg. **15**: 191-194, July, 1952.

Spina Bifida 8355. Schwidde, J. T.: Spina Bifida, Am. J. Dis. Child. **84**: 35-51, July, 1952.

Spleen, Absence 8356. Polhemus, D. W., & Schafer, W. B.: Congenital absence of the spleen; syndrome with atrioventricularis and situs inversus, Pediatrics **9**: 696-708, June, 1952.

Streptomycin. See Nos. 8301 and 8378.

Stridor, Congenital 8357. Stutsman, A. C.: Congenital laryngeal stridor, Postgrad. Med. **12**: 174-176, Aug., 1952.

Sturge-Weber Disease. See No. 8221.

Subluxation Radial Head 8358. Schmitt, H.: Ueber die durch zugbedingte schmerzhafte Armlähmung bei Kleinkindern, Med. Klin. **47**: 867-868, June 27, 1952.

Syphilis 8359. Nelson, N. A., & Struve, V. R.: The prevention of congenital syphilis, Am. J. Syph. **36**: 346-352, July, 1952.

Teaching 8360. Luzzatti, L., et al.: A training program for pediatric residents in child development and guidance, J. Pediat. **41**: 86-93, July, 1952.

Teeth 8361. Sandler, H. C.: The need for continuous dental treatment in elementary school children, Am. J. Pub. Health **42**: 972-973, Aug., 1952.

8362. Knutson, J. W.: Fluoridation of public drinking waters, South M. J. **45**: 748-755, Aug., 1952.

8363. Mellanby, H.: Dental conditions with associated signs of nutritional deficiencies in Newfoundland children, Arch. Dis. Childhood **27**: 273-282, June, 1952.

Terramycin. See No. 8297.

Testosterone. See Nos. 8319 and 8320.

Thyroid, Hyperplasia 8364. Saye, E. B., et al.: Congenital thyroid hyperplasia in twins, J. A. M. A. **149**: 1399, Aug. 9, 1952.

Tonsillectomy 8365. Phelps, K. A.: Minimizing the dangerous complications of tonsillectomy and adenoidectomy in children, Rocky Mountain M. J. **49**: 594-597, July, 1952.

Tonsils 8366. Leiber, B.: Zur Alterbiologie der Tonsillenhypertrophie, Monatsschr. Kinderh. **100**: 259-263, May, 1952.

Torticollis, Congenital 8367. Imhäuser, G.: Zur Aetiologie und Pathogenese des muskulären Schiefhalses, Ztschr. Orthop. **82**: 254-262, 1952.

Toxicosis 8368. Sacrez, R., et al.: Etude de quelques aspects des troubles circulatories au cours de la dyspepsie du nourrisson, Arch. franç. pédiat. **9**: 644-653, 1952.

Toxoplasmosis 8369. Peltonen, T.: Toxoplasmosis, Ann. med. int. Fenniae **41**: 127-133, 1952.

8370. Adams, F. H.: Toxoplasmosis in children, Postgrad. Med. **12**: 93-96, July, 1952.

8371. Hertzberg, R.: Toxoplasmosis: a review with a report of three cases, M. J. Australia **2**: 45-48, July 12, 1952.

Tracheo-esophageal Fistula 8372. Roy, F., & Lapointe, D.: Un cas de fistule trachéo-oesophagienne d'origine congénitale, Laval méd. **17**: 748-753, June, 1952.

Trichocephaliasis 8373. Kourí, P., et al.: Recientes adquisiciones en la clinica y en la terapeutica de la tricocefaliasis infantile, Revista Kuba **8**: 4-5, Jan., Feb., Mar., 1952.

Tuberculin Tests 8374. Schmid, F.: Ist die Tuberkulinreaktion morphologisch specifisch? Ztschr. Kinderh. **71**: 154-161, 1952.

Tuberculosis 8375. Lincoln, E. M., et al.: Early diagnosis and treatment of tuberculosis in children, Pediatrics **9**: 791-800, June, 1952.

8376. Kassowitz, K. E.: A reformed mealtime schedule, Wisconsin M. J. **51**: 674-677, July, 1952.

Tuberculosis, B.C.G. vaccination 8377. James, T.: Tuberculous pulmonary infiltration as a sequel to B.C.G. vaccination, Brit. J. Tuberc. **46**: 166-167, July, 1952.

Tuberculosis, Miliary 8378. Chaptal, J., et al.: Etude des miliares pulmonaires tuberculeuses traitées par la streptomycine, Montpellier médical **41/42**: 117-150, Mar.-Apr., 1952.

Tumors 8379. MacKeith, R.: Cancer in children, Guy's Hosp. Gaz. **66**: 271-281, July 12, 1952.

8380. Betke, K.: Die Cytologie des unspezifischen Lymphoms im Kindesalter, Monatsschr. Kinderh. **100**: 292-299, June, 1952.

Tumor, Adrenal 8381. Riedel, H. A.: Adrenogenital syndrome in a male child due to Adrenocortical tumor, Pediatrics **10**: 19-27, July, 1952.

8382. Neill, C., & Smith, G.: Bilateral phaechromocytoma in a 6-year-old boy, Arch. Dis. Childhood **27**: 286-290, June, 1952.

8383. Wilkins, L., & Ravitch, M. M.: Adrenocortical tumor arising in the liver of a three-year-boy with signs of virilism and Cushing's syndrome, Pediatrics **9**: 671-681, June, 1952.

Tumor, Bladder 8384. Higgins, T. T.: Rhabdo-myosarcoma of the bladder, Brit. J. Urol. **24**: 158-159, June, 1952.

Tumor, Bone 8385. Lichtenstein, L., & Hall, J. E.: Periosteal chondroma, J. Bone & Joint Surg. **34A**: 691-697, July, 1952.

Tumor, Mesentery. See No. 8136.

Tumor, Sacrococcygeal 8386. Piet, M. H.: Tumeur sacro-coccygienne (chordome) opérée chez un nouveau-né, Gynéc. et obst. **4**: 358-360, 1952.

Tumor, Spinal 8387. Hoff, H., & Weingarten, K.: Ueber spinale Tumoren im Kindesalter, Wien. Klin. Wchnschr. **64**: 220-222, March 21, 1952.

Tumor, Tongue. See No. 8382.

Turner's Syndrome 8388. James, T.: Turner's syndrome in a male infant, Edinburgh M. J. **59**: 344-354, July, 1952.

Typhoid Fever 8389. Burton, I. F., & McDermott, M.: Observations of the efficacy of chloramphenicol (Chloromycetin) and ACTH in the treatment of typhoid fever in children, J. Michigan M. Soc. **51**: 865-868, July, 1952.

Vaginitis 8390. McLean, C. C.: Penicillin suppository treatment of vulvovaginitis in children, South. M. J. **45**: 741, Aug., 1952.

Virus Infections 8391. Chaptal, J., et al.: Étude de 47 cas de grippe biologiquement confirmée par la réaction de Hirst, Montpellier Médical **41/42**: 151-193, Mar.-Apr., 1952.

Vital Capacity 8392. Ferris, B. G., et al.: Maximum breathing capacity and vital capacity of male children and adolescents, Pediatrics **9**: 659-670, June, 1952.

Vitamin A 8393. Bisaz, S.: Eine Methode zur Bestimmung des Vitamins A im Blut, Schweiz. med. Wchnschr. **82**: 692-694, June 28, 1952.

Vitamin A Deficiency 8394. Cornfeld, D., & Cooke, R. E.: Vitamin A deficiency: case report, Pediatrics **10**: 33-39, July, 1952.

Vitamin B_{12}. See No. 8203.

Wasp Stings 8395. James, E. S., & Walker, W. G.: ACTH in the treatment of multiple wasp stings, Canad. M. A. J. **67**: 50-51, July, 1952.

Xanthomatosis 8396. Nilsby, I.: Juvenile xanthoma, Acta paediat. **41**: 373-380, July, 1952.

Xanthomatosis, Biliary 8397. MacMahon, H. E.: Die biliáre Xanthomatose bei Erwachsenen und Kindern, Virchows Arch. path. Anat. **321**: 664-668, 1952.

Yaws 8398. Hasselmann, C. M.: Experimental evidence and clinical studies as basis for nomenclature in frambesia tropica (yaws), Arch. Dermat. & Syph. **66**: 107-122, July, 1952.

Current Pediatric References

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From the Department of Pediatrics, Marquette University, School of Medicine, Milwaukee, Wis.

Abdominal Pain 8399. Symposium—Abdominal Pain, M. J. Australia **2**: 115-121, July 26, 1952.

Acrodynia 8400. Najman, E., & Ćetković, S.: Beitrag zur Frage der Aetiologie der Akrodynie infolge Quecksilberüberempfindlichkeit, Ann. paediat. **179**: 81-90, Aug., 1952.

Acro-osteolysis 8401. Giaccai, L.: Familial and sporadic neurogenic acro-osteolysis, Acta radiol. **38**: 17-29, July, 1952.

ACTH 8402. Guerra, A. U. R.: ACTH y cortisona en clinica de niños, Arch. pediat. Uruguay **23**: 386-403, June, 1952.

See Nos. 8569, 8596, 8650, 8655, and 8695.

Adolescence 8403. Graham, H. B.: The problem of adolescence, M. J. Australia **2**: 136-137, July 26, 1952.

8404. Wilkins, L.: Constitutional variations of adolescent development, Mississippi Doctor **30**: 107-110, Sept., 1952.

8405. Blom, G. E.: Ambivalence and resistance to treatment in a delinquent adolescent boy, Am. J. Orthopsychiat. **22**: 584-606, July, 1952.

Adrenal, Hyperplasia 8406. Wilkins, L., et al.: Further studies on the treatment of congenital adrenal hyperplasia with cortisone, J. Clin. Endocrinol. **12**: 1015-1030, Aug., 1952.

8407. Walters, W.: Surgical treatment of hyperfunctioning lesions of the adrenal cortex, Bull. Ayer. Clin. Lab. **4**: 77-92, May, 1952.

Agranulocytosis 8408. Moeschlin, S., & Wagner, K.: Agranulocytosis due to the occurrence of leukocyte-agglutinins, Acta haemat. **8**: 29-41, July-Aug., 1952.

Albers-Schönberg Disease. See Osteopetrosis.

Allergy 8409. Pounders, C. M.: The life cycle of the allergic individual, South. M. J. **45**: 857-861, Sept., 1952.

8410. Schreiner, K.: Gedanken zur Ekzem- und Allergieforschung, Deutsche med. Wchnschr. Allergie Supp. **1**: 5-7, Aug. 15, 1952.

8411. Pisani, S., et al.: Importancia de la alergia alimentaria en los niños asmaticos, Semana méd. **59**: 54-61, July 10, 1952.

Allergy, Milk 8412. Walker, W. F.: Milk allergy, Brit. M. J. **2**: 374-375, Aug. 16, 1952.

Anemia, Aplastic. See Nos. 8460 and 8461.

Anemia, Hemolytic 8413. Cathie, I. A. B.: Apparent idiopathic Heinz body anaemia, Great Ormond Street J. No. 3: 43-48, June, 1952.

8414. Zelenik, J. S., et al.: Studies on Rh. I. Evaluation of antihuman globulin serum in the hemolytic disease of the newborn, Am. J. Obst. & Gynec. **64**: 365-370, Aug., 1952.

8415. Bauza, C. A., et al.: Un caso de enfermedad hemolitica del recien nacido con doble isoinmunizacion Rh y ABO, Arch. pediat. Uruguay **23**: 383-385, June, 1952.

See No. 8650.

Anemia, Mediterranean 8416. Astaldi, G., & Tolentino, P.: Physiopathologie et clinique de la Thalassémie, Sang **23**: 453-468, No. 6, 1952.

Anemia, Megaloblastic 8417. Colebatch, J. H., & Williams, A. L.: Megaloblastic anemia of infancy, M. J. Australia **2**: 121-123, July 26, 1952.

Anemia, Prematurity 8418. Tuttle, A. H., & Etteldorf, J. N.: Molybdenized ferrous sulfate (Mol-Iron) in the treatment of the anemia of premature infants, J. Pediat. **41**: 170-175, Aug., 1952.

Anemia, Sickle-Cell 8419. Hill, F. S., & Davis, B. C.: Further electroencephalographic studies in sickle-cell anemia, Am. J. Dis. Child. **84**: 214-217, Aug., 1952.

8420. Bartsokas, S., et al.: L'anemia a hematies falciformes chez l'homme blanc, Arch. franç. pédiat. **9**: 709-710, No. 7, 1952.

Anesthesia 8421. Eather, K. F.: The common hazards of general anesthesia for tonsillectomy and adenoidectomy, Northwest Med. **51**: 671-673, Aug., 1952.

Anomalies 8422. Behrman, S.: Genesis of fetal abnormalities, GP **6**: 41-48, Aug., 1952.

8423. Giraud, P.: A propos de l'origine des malformations congénitales, Presse méd. **60**: 1125-1126, Aug. 16, 1952.

8424. Lelong, M., et al.: Une observation anatomo-clinique d'enbryopathie rubéolique avec malformations multiples, Arch. franç. pédiat. **9:** 740-742, No. 7, 1952.

Anomalies, Abdominal Muscles 8425. Greene, L. F., et al.: Congenital absence of abdominal muscles with urologic complications: a further report, Proc. Staff Meet., Mayo Clinic **27:** 325-327, July 30, 1952.

Anomalies, Anorectal 8426. Moore, T. C., & Lawrence, E. A.: Congenital malformations of the rectum and anus. 1. Clinical features and surgical management in 120 cases, Surgery **32:** 352-366, Aug., 1952.

8427. Moore, T. C., & Lawrence, E. A.: Congenital malformations of the rectum and anus. 2. Associated anomalies encountered in a series of 120 cases, Surg., Gynec. & Obst. **95:** 281-288, Sept., 1952.

Anomalies, Bile Duct 8428. MacMahon, H. E., & Thannhauser, S. J.: Congenital dysplasia of the interlobular bile ducts with extensive skin xanthomata: congenital acholangic biliary cirrhosis, Gastroenterology **21:** 488-506, Aug., 1952.

Anomalies, Eye 8429. Donahue, H. C.: Congenital ectasia of the cornea, Arch. Ophth. **48:** 154-160, Aug., 1952.

Anomalies, Genitourinary 8430. Gross, R. E., & Cresson, S. L.: Treatment of epispadias: a report of 18 cases, J. Urol. **68:** 477-488, Aug., 1952.

8431. Wolgin, W., et al.: Co-existence of congenital median bar and urethral valves, J. Urol. **68:** 506-509, Aug., 1952.

8432. O'Brien, H. A., & Mitchell, J. D., Jr.: Ectopic ureteral orifice. Report of 5 cases, New Orleans M. & S. J. **104:** 585-589, Aug., 1952.

Anomalies, Kidney 8433. Allemann, R.: Die Chirurgie der Missbildungen der obern Harnwege, Helvet. chir. acta **19:** 201-232, No. 3, 1952.

See No. 8425.

Anomalies, Nose 8434. Whitehouse, W. M., & Holt, J. F.: Paradoxical expiratory ballooning of the hypopharynx in siblings with bilateral choanal atresia, Radiology **59:** 216-220, Aug., 1952.

Antibiotics 8435. Karelitz, S.: Etat actuel du traitement de quelques maladies infectieuses de l'enfant par les antibiotiques et les sulfamides, Arch. franç. pédiat. **9:** 673-688, No. 7, 1952.

Antihyaluronidase. See No. 8436.

Antistreptolysin 8436. Rantz, L. A., et al.: Antistreptolysin O and antihyaluronidase titers in health and in various diseases, Am. J. M. Sc. **224:** 194-200, Aug., 1952.

Appendicitis 8437. Deaver, J. M.: Acute appendicitis in children, Ann. Surg. **136:** 243-249, Aug., 1952.

8438. Gilmour, I. E. W., & Lowdon, A. G. R.: Acute appendicitis, Edinburgh M. J. **59:** 361-373, Aug., 1952.

8439. Rubnitz, M. E., & Hansen, J. L.: The clinical and pathologic aspects of appendicitis, U. S. Armed Forces M. J. **3:** 1359-1361, Sept., 1952.

8440. Miller, E. M., & Bryant, R.: Mesenteric venous thrombosis associated with acute appendicitis in a young child. Recovery following resection of infarcted intestine, J. A. M. A. **149:** 1634-1636, Aug. 30, 1952.

Arthritis. See No. 8591.

Asthma 8441. Panzani, R.: Le diagnostic biologique de l'allergie naso-sinusienne et tracheo-bronchique chez l'enfant, Pédiatrie **41:** 615-626, No. 5, 1952.

8442. Pisani, S., et al.: Importancia de la alergia alimentaria en los niños asmaticos, Semana méd. **59:** 136-138, July 24, 1952.

See No. 8411.

Atrophy, Nutritional 8443. Barta, L., & Kukács, F. V.: Beiträge zum Zuckerstoffwechsel atrophischer Säuglinge, Ann. paediat. **179:** 91-99, Aug., 1952.

Autonomic Dysfunction, Familial 8444. Riley, C. M.: Familial autonomic dysfunction, J. A. M. A. **149:** 1532-1535, Aug. 23, 1952.

Behaviour Problems 8445. Black, I. S.: Everyday problems of the preschool child, J. Pediat. **41:** 233-243, Aug., 1952.

8446. Timme, A. R.: What has neurology to offer child guidance? Neurology **2:** 435-440, Oct., 1952.

Bile Duct, Atresia 8447. Swenson, O., & Fisher, J. H.: Utilization of cholangiogram during exploration for biliary atresia, New England J. Med. **247:** 247-248, Aug. 14, 1952.

See No. 8556.

Birth Injury. See No. 8515.

Bladder Exstrophy 8448. Gross, R. E., & Cresson, S. L.: Exstrophy of bladder. Observations from 80 cases, J. A. M. A. **149:** 1640-1644, Aug. 30, 1952.

8449. Williams, D. I., & Jolly, H. R.: Long term results of transplantation of the ureters for ectopia vesicae, Great Ormond Street J. No. 3: 9-13, June, 1952.

Bornholm's Disease 8450. Bury, H. S., & Tobin, J. O'H.: Further outbreak of Bornholm disease associated with Coxsackie virus, Lancet **2:** 267-269, Aug. 9, 1952.

8451. Van Creveld, S.: La maladie de Bornholm, Arch. franç. pédiat. **9:** 689-697, No. 7, 1952.

Burns 8452. Simonart, A.: New advances in the pathology of burns, Tr. & Stud. Coll. Physicians, Philadelphia **20:** 50-57, Aug., 1952.

8453. Choy, D. S. J., & Wendt, W. E.: A new local treatment of burns, U. S. Armed Forces M. J. **3:** 1241-1255, Sept., 1952.

Calcification, Intra-abdominal 8454. Kasmersky, C. T., & Howard, W. H. R.: The significance of intra-abdominal calcification in the newborn infant, Am. J. Roentgenol. **68:** 395-398, Sept., 1952.

Carob Flour. See No. 8482.

Cat-Scratch Fever 8455. Gifford, H.: Cat scratch fever, Stanford M. Bull. **10:** 157-161, Aug., 1952.

See No. 8496.

Celiac Disease 8456. Payne, W. W.: Laboratory tests in the diagnosis of coeliac and fibrocystic disease, Great Ormond Street J. No. 3: 23-32, June, 1952.

Cephalhematoma 8457. Kendall, N., & Woloshin, H.: Cephalhematoma associated with fracture of the skull, J. Pediat. **41:** 125-132, Aug., 1952.

Cerebral Hemorrhage. See No. 8586.

Cerebral Injury. See No. 8605.

Cerebral Palsy 8458. Medalie, M.: Rehabilitation of the cerebral palsy child at the Forest Town School, Johannesburg, South African M. J. **26:** 569-573, July 12, 1952.

Cerebral Palsy, Familial 8459. Adler, E.: Familial cerebral palsy, Monatsschr. Psychiat. u. Neurol. **124:** 8-21, July, 1952.

Chloromycetin Reactions 8460. Hawkins, L. A., & Lederer, H.: Fatal aplastic anaemia after chloramphenicol treatment, Brit. M. J. **2:** 423-426, Aug. 23, 1952.

8461. Wolman, B.: Fatal aplastic anaemia after chloramphenicol, Brit. M. J. **2:** 426-427, Aug. 23, 1952.

Cholecystitis 8462. Gibbon, G. W.: Acute, sub-acute and chronic cholecystitis in a 20-month-old infant, Canad. M. A. J. **67:** 150, Aug., 1952.

Cholelithiasis 8463. Snyder, W. H., Jr., et al.: Cholelithiasis and perforation of the gallbladder in an infant, with recovery, J. A. M. A. **149:** 1645-1646, Aug. 30, 1952.

Chondrodystrophy 8464. Grebe, H.: Zur Differentialdiagnose und Aetiologie multipler Epiphysenstörungen, Ztschr. Kinderh. **71:** 243-267, No. 3, 1952.

Cirrhosis 8465. Adams, F. H., et al.: Four siblings with hepatic disease leading to cirrhosis, Am. J. Dis. Child. **84:** 168-174, Aug., 1952.

8466. Path. Case No. 701—Jaundice, Case Reports Child. Mem. Hosp. Chicago, Ill. **10:** 3059-3062, July, 1952.

8467. Bleckmann, K. H.: Beitrag zum Problem der kindlichen familiären Lebercirrhose, Ztschr. Kinderh. **71:** 222-242, No. 3, 1952.

See No. 8428.

Cleft Palate 8468. Matthews, D. N.: The premaxilla in bilateral clefts of lip and palate, Brit. J. Plast. Surg. **5:** 77-86, July, 1952.

Convulsions 8469. Ariztia, A.: Convulsiones en la infancia, Arch. pediat. Uruguay **23:** 354-379, June, 1952.

Cortisone. See Nos. 8402, 8596, 8650, and 8695.

Coxsackie Virus Disease 8470. Huebner, R. J., et al.: The importance of Coxsackie viruses in human disease, particularly herpangina and epidemic pleurodynia, New England J. Med. **247:** 249-256, Aug. 14, 1952.

8471. Carpenter, C. M., & Boak, R. A.: Coxsackie viruses, California Med. **77:** 127-130, Aug., 1952.

8472. Berger, E., et al.: Zur Kenntnis der Coxsackie-virus (C-virus) infektionen, Ann. paediat. **179:** 65-80, Aug., 1952.

See Nos. 8450 and 8632.

Cyst, Intestine. See No. 8552.

Cyst, Lung 8473. Whitesell, F. B., Jr., & White, W. J.: Congenital cystic disease of the lung in the newborn, Ann. Surg. **136:** 299-304, Aug., 1952.

Cyst, Nose 8474. Champion, R., & Prendiville, J. B.: Dermoid cyst of the nose, Brit. J. Plast. Surg. **5:** 94-97, July, 1952.

Cystinosis 8475. King, W. B., Jr.: An anatomic study of a case of cystinosis, Stanford M. Bull. **10:** 162-172, Aug., 1952.

8476. Verger, P., et al.: Cystinurie, lithiase cystinique et cystinose; à propos de deux observations récentes, Arch. franç. pédiat. **9:** 776-780, No. 7, 1952.

Dermatitis, Exfoliative 8477. Lee, H. F., et al.: Impetigo and acute infectious exfoliative dermatitis of the newborn infant (Ritter's disease), J. Pediat. **41:** 159-169, Aug., 1952.

Dermatitis, Herpetiformis 8478. Berlin, C.: Dermatitis herpetiformis in children, Brit. J. Dermat. **64:** 281-290, July-Aug., 1952.

Diabetes 8479. Mayer, J. B.: Die Embryopathia diabetica, Ztschr. Kinderh. **71:** 183-201, No. 3, 1952.

Diarrheal Diseases 8480. Walker, S. H.: Polymyxin B in pseudomonas and proteus enteritis, J. Pediat. **41:** 176-181, Aug., 1952.

8481. Gabroy, H. K., & Horoschak, S.: The treatment of diarrheal syndrome with Resion, Rev. Gastroenterol. **19:** 660-661, Aug., 1952.

8482. Abella, P. U.: Treatment of acute infantile diarrhea with carob flour (Arobon), J. Pediat. **41:** 182-187, Aug., 1952.

8483. Braun, O. H., & Henckel, H.: Säuglingsenteritis durch pathogene Colitypen, insbesondere E. coli 55/B 5, Ztschr. Kinderh. **71:** 273-285, No. 3, 1952.

8484. Schlesinger, B., & Welch, R. G.: Quadraplegia complicating gastroenteritis, Great Ormond Street J. No. 3: 14-19, June, 1952.

8485. Chattas, A.: El formaldehidosulfatiazol en la enteritis infecciosa del niño, Semana méd. **59:** 8-10, July 3, 1952.

Dormison 8486. Malone, H. J., et al.: A study of the hypnotic effect of Dormison in children, J. Pediat. **41:** 153-158, Aug., 1952.

Dyschondroplasia. See No. 8513.

Dysentery 8487. Geiger, J. C.: Paratyphoid (salmonella) in the Bay region of California, Arch. Pediat. **69:** 288-290, July, 1952.

Dysostosis, Craniofacial 8488. Chaptal, J., et al.: Maladie de Crouzon: intérêt du traitement chirurgical, Arch. franç. pédiat. **9:** 747-753, No. 7, 1952.

Dyspepsia, Newborn 8489. Jorup, S.: Colonic hyperperistalsis in neurolabile infants, Acta paediat. **41:** Suppl. 85, April, 1952.

Eczema 8490. Hill, L. W.: Nomenclature, classification, and pathogenesis of eczema in infancy, Arch. Dermat. & Syph. **66:** 212-222, Aug., 1952.

See No. 8557.

Eczema Varicelliform, Diphtheretic 8491. LeCoulant, et al.: La diphtérie cutaneé varicelliforme du nourrisson, Arch. franç. pédiat. **9:** 770-772, No. 7, 1952.

Electrocardiography 8492. Lamb, L. E., & Dimond, E. G.: The spatial vectorcardiogram during the first decade of life, Am. Heart J. **44:** 174-183, Aug., 1952.

See No. 8636.

Electroencephalography 8493. Melin, K-A.: Elektroencephalographische Untersuchungen an angiokardiographierten Patienten, Ztschr. Kinderh. **71:** 301-306, No. 3, 1952.

Electrolyte Balance 8494. Forbest, G. B.: Chemical growth in infancy and childhood, J. Pediat. **41:** 202-232, Aug., 1952.

Electromyography 8495. Luder, J.: The value of electromyography in paediatries, Great Ormond Street J. No. 3: 1-8, June, 1952.

Encephalitis, Cat-Scratch 8496. Stevens, H.: Cat-scratch fever encephalitis, Am. J. Dis. Child. **84:** 218-222, Aug., 1952.

Encephalitis, Measles 8497. Clin. Case No. 698—Measles encephalitis, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3053, July, 1952.

8498. Clin. Case No. 697—Measles encephalitis, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3051-3052, July, 1952.

Encephalomeningocele 8499. Moore, P. M.: Intranasal encephalomeningocele, Laryngoscope **62:** 659-677, July, 1952.

Encopresis 8500. Reed, R. E.: A case of anal character formation, Delaware M. J. **24:** 204-206, Aug., 1952.

Endocardial Fibroelastosis 8501. Adams, F. H., & Katz, B.: Endocardial fibroelastosis, J. Pediat. **41:** 141-152, Aug., 1952.

Eosinophil 8502. Cape, R. D. T.: The eosinophile cells of the blood, Edinburgh M. J. **59:** 374-384, Aug., 1952.

Eosinophilic Granuloma 8503. Bynum, G. A.: Eosinophilic granuloma of the skull, Am. Surgeon 18: 793-805, Aug., 1952.

Epidermolysis Bullosa 8504. Kagen, M. S., et al.: Epidermolysis bullosa hereditaria in a newborn. Report of two cases, Wisconsin M. J. **51:** 766-767, Aug., 1952.

Epilepsy 8505. Loscalzo, A. E.: Mesantoin in the control of epilepsy, Neurology **2:** 403-411, Oct., 1952.

8506. Paillas, J. E., et al.: L'épilepsie en foyer de l'enfant, Rev. neurol. **86:** 300-318, No. 4, 1952.

Erythroblastosis 8507. Cawley, E. P.: Herpes gestationis and the Rh factor, South. M. J. **45:** 827-832, Sept., 1952.

8508. Potter, E. L.: The practical aspects of the Rh factor, Minnesota Med. **35:** 729-731 & 773, Aug., 1952.

8509. Bryce, L. M., et al.: The role of ABO incompatability as a cause of erythroblastosis foetalis, with report of a case, M. J. Australia **2:** 77-79, July 19, 1952.

Erythroderma Desquamativa 8510. Mester, A., et al.: Funktionelle und anatomische Pankreasveränderungen bei Erythrodermia desquamative Leineri, Arch. Kinderh. **145:** 59-65, No. 1, 1952.

Esophagus, Atresia 8511. Dabadie, J.: Un cas d'atrésie congénitale de l'oesophage. Guérison chirurgicale, Arch. franç. pédiat. **9:** 764-767, No. 7, 1952.

Esophagus, Dilatation 8512. De Weese, D. D.: Esophageal dilatation, Portland Clin. Bull. **6:** 35-40, Sept., 1952.

Exostoses, Multiple 8513. Stark, J. D., et al.: Hereditary multiple exostoses, Radiology **59:** 212-215, Aug., 1952.

Fibrocystic Disease. See No. 8456.

Fracture, Forearm 8514. Giberson, R. G., & Ivins, J. C.: Fractures of the distal part of the forearm in children. Correction of deformity by growth, Minnesota Med. **35:** 744-749, Aug., 1952.

Fracture, Temporomandibular 8515. Turner, A. M.: A case of birth fracture involving the right temporo-mandibular articulation, Great Ormond Street J. No. 3: 68-71, June, 1952.

Gargoylism. See No. 8464.

Goiter, Congenital 8516. Moran, T. J.: Congenital goiter with death from milk-aspiration pneumonia, Arch. Path. **54**: 213-219, Aug., 1952.

Growth 8517. Forbes, H. A. W.: The assessment of growth in disease. The use of Wetzel's grid illustrated by rheumatic fever, Lancet **2**: 224-225, Aug. 2, 1952.

8518. Garn, S. M.: Physical growth and development, Am. J. Phys. Anthropol. **10**: 169-192, June, 1952.

See No. 8604.

Heart, Dynamics 8519. Hockerts, Th.: Utersuchungen über die Dauer der isometrischen kontraktionsphase des gesunden kindlichen Herzens, Ztschr. Kinderh. **71**: 216-221, No. 3, 1952.

Heart Disease, Congenital 8520. Adelman, M. H., et al.: Anesthetic management in cardiac catheterization and angiocardiography, New York J. Med. **52**: 1866-1870, Aug. 1, 1952.

8521. Jönsson, G., & Saltzman, G-F.: Infundibulum of patent ductus arteriosus—a diagnostic sign in conventional roentgenograms, Acta radiol. **38**: 8-16, July, 1952.

8522. Lewes, D.: The exercise test in patent ductus arteriosus, Brit. Heart J. **14**: 357-362, July, 1952.

8523. Henry, G. W.: The roentgen diagnosis of dextroposition of the aorta, Am. J. Roentgenol. **68**: 386-390, Sept., 1952.

8524. Burchell, H. B., & Pugh, D. G.: Uncomplicated isolated dextrocardia "dextroversio cordis" type, Am. Heart J. **44**: 196-206, Aug., 1952.

8525. Moscovitz, H. L., et al.: Levocardia, Am. Heart J. **44**: 184-195, Aug., 1952.

8526. Elyan, M., & Ruffle, F. C.: Two cases of complete transposition of the great vessels of the heart, M. J. Australia **2**: 91-92, July 19, 1952.

8527. Cudkowicz, L., & Armstrong, J. B.: Injection of the bronchial circulation in a case of transposition, Brit. Heart J. **14**: 374-378, July, 1952.

8528. D'Abreu, A. L., et al.: Double aortic arch treated surgically, Brit. J. Surg. **40**: 70-73, July, 1952.

8529. Schultz, F. B.: An unusual congenital cardiac anomaly with associated anomalous venous return: sudden death, Am. Pract. **3**: 616-621, Aug., 1952.

8530. Snow, P. J. D.: Tricuspid atresia: a new radioscopic sign, Brit. Heart J. **14**: 387-390, July, 1952.

8531. Campbell, M., et al.: Cor biloculare, Brit. Heart J. **14**: 317-324, July, 1952.

See No. 8658.

Heinz Body Anemia. See No. 8413.

Hemangioma 8532. Michel, P.-J.: Un cas d'angiomatose maligne extensive, à tendance ulcéro-nécrotique chez un nourrisson. Terminaison mortelle, Bull. Soc. franç. dermat. et syph. **59**: 180, Mar.-Apr., 1952.

Hematoma, Subdural 8533. Sulamaa, M., & Vara, P.: An investigation into the occurrence of perinatal subdural haematoma; its diagnosis and treatment, Acta obst. et gynec. scandinav. **31**: 400-412, No. 4, 1952.

Hemiplegia 8534. Corcos, A., & Tabbane, C.: Hémiplégie droite avec aphasie au cours d'une coqueluche chez un enfant de 2 ans 1/2. Guérison, Arch. franç. pédiat. **9**: 742-743, No. 7, 1952.

8535. Chaptal, J., et al.: Hémiplégie par thrombose artérielle au cours de l'évolution d'une méningite tuberculeuse de l'enfant. Rechute et mort en état de méningo-di-encéphalite. Confrontation clinique, électro-encéphalographique et anatomique, Arch. franç. pédiat. **9**: 727-738, No. 7, 1952.

8536. Laine, E., et al.: Étude d'une série d'hémisphérectomies pour hémiplégie infantile, Rev. neurol. **86**: 344-350, No. 4, 1952.

Hemorrhagic Diseases 8537. Schulman, I., & Smith, C. H.: Hemorrhagic disease in an infant due to deficiency of a previously undescribed clotting factor, Blood **7**: 794-807, Aug., 1952.

Hernia, Diaphragmatic 8538. Ebbs, J. H., & McGarry, H. H.: Congenital hernia of the diaphragm, Canad. M. A. J. **67**: 115-117, Aug., 1952.

8539. McGuire, E. J., & Hinkel, C. L.: Congenital diaphragmatic hernias, Bull. Geisinger Mem. Hosp. **4**: 104-111, Aug., 1952.

8540. Clin. Case No. 696—Diaphragmatic hernia, Case Reports, Child. Mem. Hosp. Chicago, Ill. **10**: 3049-3051, July, 1952.

8541. Arnheim, E. E.: Congenital hernia of the diaphragm with special reference to right-sided hernia of the liver and intestines, Surg., Gynec. & Obst. **95**: 293-307, Sept., 1952.

Hernia, Inguinal 8542. Hendrick, J. A.: Surgical repair of hernia in children, New Orleans M. & S. J. **104**: 566-569, Aug., 1952.

Herpangina. See No. 8470.

Herpes Simplex 8543. Finberg, L., & Easton, R. S.: Generalized cutaneous herpes simplex, J. Pediat. **41**: 188-191, Aug., 1952.

Hip Disease 8544. Sherman, M. S.: Diagnosis of hip disease in children, J. Am. M. Women's A. **7**: 283-293, Aug., 1952.

Hospitalism 8545. Fischer, L. K.: Hospitalism in a six-month-old infant, Am. J. Orthopsychiat. **22:** 522-533, July, 1952.

8546. Jackson, K., et al.: Problem of emotional trauma in hospital treatment of children, J. A. M. A. **149:** 1536-1538, Aug. 23, 1952.

Hydrogen Ions 8547. Bradley, J. E., & Tilghman, M.: In situ hydrogen ion measurements of the mouth, esophagus and stomach in newborn infants, Am. J. Digest. Dis. **19:** 255-257, Aug., 1952.

Hypertension 8548. Kappert, A.: Der jugendliche Hochdruck, Schweiz. med. Wchnschr. **82:** 821-825, Aug. 16, 1952.

Hypervitaminosis A 8549. Goldzier, S. E., et al.: Hypervitaminosis A, J. Pediat. **41:** 198-201, Aug., 1952.

Inclusion Diseases. See No. 8699.

Insect Bites 8550. Rockwell, E. M.: Some investigational studies concerning reactions to insect bites, Ann. Allergy **10:** 404-410, July-Aug., 1952.

Intestine, Duplication 8551. Fox, R. T., & Fowler, J. T., Jr.: Duplication of the alimentary tract, J. Pediat. **41:** 194-197, Aug., 1952.

8552. Clin. Case No. 703—Large abdomen; difficult breathing, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3070-3073, Aug., 1952.

8553. Davis, J. E., & Barnes, W. A.: Intrathoracic duplications of the alimentary tract communicating with the small intestine, Ann. Surg. **136:** 287-295, Aug., 1952.

8554. Hardaway, R. M., et al.: Duplication of the terminal ileum, Ann. Surg. **136:** 296-298, Aug., 1952.

Intestine, Obstruction 8555. Clin. Case No. 706—Intestinal obstruction, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3078-3080, Aug., 1952.

Jaundice 8556. Kiesewetter, W. B. & Koop, C. E.: The surgeon's role in the management of obstructive jaundice in infancy, Bull. Ayer Clin. Lab. **4:** 55-60, May, 1952.

Also see Cirrhosis, Bile Duct Atresia, etc.

Kaposi's Varicelliform Eruption 8557. Clin. Case No. 705—Eczema and Kaposi's eruption, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3075-3077, Aug., 1952.

See No. 8491.

Keratoderma 8558. Bataille, R., & Duperrat, M.: La dentition dans les kératodermies palmo-plantaires congénitales, Bull. Soc. franç. dermat. et syph. **59:** 121-123, Mar.-Apr., 1952.

Kidney 8559. Pygott, F.: Intracapsular tear of the lower pole of kidney, Brit. J. Radiol. **25:** 449, Aug., 1952.

Kidney, Function Tests 8560. Barclay, J. A., et al.: Renal tubular reabsorption, Acta med. scandinav. **143:** 361-364, No. 5, 1952.

8561. Bing, J.: The use of urea clearance as a test of kidney function, Acta med. scandinav. **143:** 341-349, No. 5, 1952.

Kidney, Infarction 8562. Milburn, C. L., Jr.: Hemorrhagic infarction of the kidneys in infants, J. Pediat. **41:** 133-140, Aug., 1952.

Kidney, Pneumography 8563. Gershon-Cohen, J., et al.: Retroperitoneal pneumography by injection of oxygen into the presacral space, Am. J. Roentgenol. **68:** 391-394, Sept., 1952.

Klippel-Feil Syndrome 8564. Shoul, M. I., & Ritvo, M.: Clinical and roentgenological manifestations of the Klippel-Feil syndrome (congenital fusion of the cervical vertebrae, brevicollis), Am. J. Roentgenol. **68:** 369-385, Sept., 1952.

Labyrinthitis. See No. 8662.

Laryngotracheitis 8565. Simmons, F. H.: Preventive treatment of laryngotracheobronchitis in child of twenty-two months, Arch. Otolaryng. **56:** 209-212, Aug., 1952.

Leontiasis Ossea. See No. 8609.

Leprosy 8566. Gray, J. A. C.: Some practical clinical aspects of leprosy, U. S. Armed Forces M. J. **3:** 1297-1311, Sept., 1952.

Leukemia 8567. Ward, J. E., et al.: Familial leukemia: a report of three cases of leukemia and one leukemoid reaction in one family, Am. J. Human Genet. **4:** 90-93, June, 1952.

8568. Quilligan, J. J.: Childhood malignancies. 5. Chemotherapy of leukemia, Texas J. Med. **48:** 571-575, Aug., 1952.

8569. Sharnoff, G., & Raymond, E.: Acute monocytic leukemia responsive to ACTH therapy, New York J. Med. **52:** 1911-1912, Aug. 1, 1952.

Leukemia, Congenital 8570. Riviére, M., et al.: Leucose aiguë congénitale chez un nouveau-né, Arch. franç. pédiat. **9:** 768-769, No. 7, 1952.

Lung Resection 8571. Denk, W.: Ueber Lungenresektionen im Kindesalter, Wien. med. Wchnschr. **102:** 610-611, Aug. 16, 1952.

Macroglossia 8572. Clin. Case No. 70—Large tongue, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3056-3059, July, 1952.

Mandible, Ankylosis 8573. Braithwaite, F., & Hopper, F.: Ankylosis of the temporomandibular Joint, Brit. J. Plast. Surg. **5:** 105-121, July, 1952.

Meckel's Diverticulum 8574. Thiel, J. M.: Meckel's diverticulum, Am. Surg. **18:** 826-835, Aug., 1952.

Meconium Ileus 8575. Fleury, J.: Iléus à meconium blanc avec microcôlon vermiforme sans lésion pancréatique, Arch. franç. pédiat. **9:** 725-726, No. 7, 1952.

Meconium, Peritonitis 8576. Forshall, I., et al.: Meconium peritonitis, Brit. J. Surg. **40:** 31-40, July, 1952.

8577. Tempest, M. N.: Meconium peritonitis. Report of a case due to spontaneous intra-uterine perforation of the transverse colon, with a brief review of the literature, Brit. J. Surg. **40:** 28-31, July, 1952.

8578. Franklin, A. W., & Hosford, J. P.: Meconium peritonitis due to a hole in the foetal intestinal wall and without obstruction, Brit. M. J. **2:** 257-259, Aug. 2, 1952.

Megacolon 8579. Austin, D. V.: The etiology and pathogenesis of congenital megacolon, Quart. Bull. Northwestern Univ. M. School **26:** 235-240, Fall, 1952.

8580. Hallenbeck, G. A., & Waugh, J. M.: The surgical treatment of megacolon, S. Clin. North America, pp. 1203-1216, Aug., 1952.

8581. Kirksey, O. T., Jr., & Childers, J. H.: Megacolon-frozen section control of surgical treatment, Am. Surgeon **18:** 748-750, Aug., 1952.

Meningitis, Pneumococcic 8582. Trice, P. A., & Townsend, T. E.: Meningitis due to Klebsiella pneumoniae, J. A. M. A. **149:** 1471-1473, Aug. 16, 1952.

Meningitis, Tuberculous 8583. Somner, A. R.: Tuberculous meningitis—some aspects of its treatment, Brit. M. J. **2:** 356-360, Aug. 16, 1952.

8584. Willemin-Clog, L., et al.: Le taux des chlorures du l.c.r. au cours de la méningite tuberculeuse, Pediatrie **41:** 609-612, No. 5, 1952.

See No. 8535.

Meningo-encephalitis, Mumps 8585. Clin. Case No. 704—Mumps meningo-encephalitis, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3074-3075, Aug., 1952.

Mental Deficiency 8586. Tarlov, I. M., & Grayzel, D.: Brain hemorrhage after carotid-jugular anastomosis, Ann. Surg. **136:** 250-260, Aug., 1952.

Mesenteric Thrombosis. See No. 8440.

Methemoglobinemia 8587. Campbell, W. A. B.: Methemobloginemia due to nitrates in well water, Brit. M. J. **2:** 371-373, Aug. 16, 1952.

8588. Codounis, A.: Hereditary methemoglobinemic cyanosis, Brit. M. J. **2:** 368-371, Aug. 16, 1952.

Mononucleosis, Infectious 8589. Hsia, D. Y., & Gellis, S. S.: Hepatic dysfunction in infectious mononucleosis in children, Am. J. Dis. Child. **84:** 175-183, Aug., 1952.

8590. Leibowitz, S.: Infectious mononucleosis, Am. J. Med. **13:** 172-182, Aug., 1952.

8591. Rischbieth, H. G.: A severe case of glandular fever with arthritis, Great Ormond Street J. No. 3: 72-75, June, 1952.

8592. Hoagland, R. J.: Infectious mononucleosis, Am. J. Med. **13:** 158-171, Aug., 1952.

Mortality, Infant 8593. Wellen, I.: Specific hypertensive disease of pregnancy: factors affecting infant mortality, Am. J. Obst. & Gynec. **64:** 271-280, Aug., 1952.

See No. 8605.

Muscular Dystrophy 8594. Choremis, K. B., et al.: Zur Aetiologie und Pathogenese der Dystrophie, Ztschr. Kinderh. **71:** 202-215, No. 3, 1952.

Myelodysplasia. See No. 8401.

Myocarditis 8595. Path. Case No. 702—Acute and chronic myocarditis, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3067-3070, Aug., 1952.

See No. 8635.

Myositis Ossificans 8596. Evans, P. R.: Myositis ossificans progressiva treated with cortisone and ACTH, Great Ormond Street J. No. 3: 56-63, June, 1952.

Neck, Webbed 8597. Wynn-Williams, D.: Congenital midline cervical cleft and web, Brit. J. Plast. Surg. **5:** 87-93, July, 1952.

Nephritis 8598. Clin. Case No. 699—Convulsions and anuria, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3054-3056, July, 1952.

8599. Thenebe, C. L.: Light Magnesium carbonate in the treatment of acute glomerular nephritis, Arch. Pediat. **69:** 285-287, July, 1952.

Newborn 8600. Morison, J. E.: Foetal and neonatal pathology, St. Louis, 1952, The C. V. Mosby Co., pp. 1-366.

8601. Cohen, E. N.: Resuscitation of the newborn, Minnesota Med. **35:** 750-752 & 808, Aug. 1952.

8602. Clin. Case No. 707—prolonged bleeding in a newborn, Case Reports Child. Mem. Hosp., Chicago, Ill., **10:** 3081-3082, Aug. 1952.

8603. Dahlström, E. A., et al.: Mixed infection with Staphylococcus aureus and Bacterium coli neapolitanum in a ten-day-old infant, Ann. paediat. **179:** 124-127, Aug. 1952.

8604. Giraud, P., et al.: Le traitement de la débilté congénitale et des retards de croissance du nouveau-né par la pénicilline et les filtrats placentaires, Arch. franç. pédiat. **9:** 698-708, No. 7, 1952.

8605. Knezevic, M.: Des causes de décès des nouveau-nés, Gynéc. et obst. **51:** 248-263, No. 3, 1952.

8606. Giraud, P., et al.: Le traitement de la débilité congénitale et des retards de croissance du nouveau-né par la pénicilline et les filtrats placentaires, Union méd. Canada **81:** 514-522, May, 1952.

See Nos. 8414, 8434, 8454, 8473, 8489, 8504, 8533, 8547, 8666, and 8679.

Orthodontia 8607. Caseley, R.: Malformations and Irregularities of the teeth and jaws in children, J. Roy. Inst. Pub. Health & Hyg. **15:** 204-209, Aug. 1952.

Osteomyelitis 8608. Köle, W.: Ueber das weitere Shicksal der mit Knochentrepanation und Penicillininstillation behandelten akuten Osteomyelitis, Langenbecks Arch. u. Dtsch. Z. Chir. **272:** 201-211, No. 3, 1952.

Osteopetrosis 8609. Mitchell, R. G., & MacLeod, W.: Leontiasis ossea due to Albers-Schönberg's disease, Brit. J. Radiol. **25:** 442-445, Aug. 1952.

Otitis Media 8610. Singleton, J. D.: Otitis media with effusion, South. M. J. **45:** 798-801, Sept. 1952.

Pancreas, Fibrocystic Disease 8611. Johnstone, D. E.: Studies on cystic fibrosis of the pancreas, Am. J. Dis. Child. **84:** 191-198, Aug. 1952.

8612. Clin. Case No. 695—Foul bulky stools and cough, Case Reports Child. Mem. Hosp., Chicago, Ill. **10:** 3047-3048, July, 1952.

8613. Goodman, H. O., & Reed, S. C.: Heredity of fibrosis of the pancreas, Am. J. Human Genet. **4:** 59-71, June, 1952.

8614. MacFarlane, J. C. W.: Serum-antithrombin level in fibrocystic disease of the pancreas, Lancet **2:** 311-314, Aug. 16, 1952.

See No. 8510.

Pericarditis 8615. Davies, D. H.: Acute benign pericarditis of unknown origin, Brit. Heart J. **14:** 309-316, July, 1952.

Pertussis 8616. LaBoccetta, A. C., & Dawson, K. E.: Pertussis, Am. J. Dis. Child. **84:** 184-190, Aug. 1952.

Phenylpyruvic Oligophrenia. See No. 8586.

Pityriasis rubra pilaris 8617. De Graciansky, P., et al.: Heureux effet du traitement par la vitamine A synthétique dans un cas de pityriasis rubra pilaire généralisé, Bull. Soc. franç. dermat. et syph. **59:** 152-153, Mar.-Apr., 1952.

Pleurodynia. See No. 8470.

Pneumonia, Aspiration. See No. 8516.

Pneumonia, Interstitial 8618. Sacrez, R., et al.: Pneumonie interstitielle a plasmocytes, Arch. franç. pédiat. **9:** 711-717, No. 7, 1952.

Pneumonia, Staphylococcus 8619. Bernheim, M., & Gaillard, L.: Les staphylococcies pleuro-pulmonaires de l'enfant, Pediatrie **41:** 629-662, No. 5, 1952.

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Poisoning 8620. Price, J. P.: Accidental poisonings in children, GP **6:** 53-60, Aug. 1952.

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Poisoning, Boric Acid 8622. Bumbalo, T. S.: Boric acid poisoning, New York J. Med. **52:** 1913-1914, Aug. 1, 1952.

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Poisoning, Lead 8625. Millichap, J. G., et al.: Lead paint: a hazard to children, Lancet **2:** 360-362, Aug. 23, 1952.

Poisoning, Mercury 8626. Swensson, A.: Investigations on the toxicity of some organic mercury compounds which are used as seed disinfectants. Acta med. scandinav. **143:** 365-384, No. 5, 1952.

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8631. Harding, H. B., et al.: What are the poliomyelitis viruses? Quart. Bull. Northwestern Univ. M. School **26:** 228-234, Fall, 1952.

8632. Melnick, J. L., & Penner, L. R.: The survival of poliomyelitis and Coxsackie viruses following their ingestion by flies, J. Exper. Med. **96:** 255-271, Sept. 1, 1952.

8633. Fox, M. J.: The 1951 epidemic of poliomyelitis in the City of Milwaukee, Wisconsin M. J. **51:** 768-771, Aug. 1952.

8634. Fox, M. J., et al.: Bulbar poliomyelitis, New England J. Med. **247:** 276-279, Aug. 21, 1952.

8635. Laruelle & Reumont: La myocardite de la poliomyélite, Ann. Inst. Pasteur **83:** 151-155, Aug. 1952.

8636. Rose, L. M.: Electrocardiographic changes in acute poliomyelitis in childhood, Brit. Heart J. **14:** 391-400, July, 1952.

8637. Pilcher, M. F.: Pes calcaneo-cavovalgus, Great Ormond Street J. No. 3: 36-42, June, 1952.

8638. Smith, E., & Rosenblatt, P.: Venospasm an early and late manifestation of poliomyelitis, Angiology **3:** 283-288, Aug. 1952.

8639. Hunley, H. C., Jr.: Air transportation of acute poliomyelitis patients, U. S. Armed Forces M. J. **3**: 1337-1340, Sept. 1952.

8640. Wolf, S. I.: Therapy of Poliomyelitis, M. Ann. District of Columbia **21**: 413-421, Aug. 1952.

8641. Kelleher, W. H., et al.: Notes on cuirass respirators, Brit. M. J. **2**: 413-415, Aug. 23, 1952.

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Protein Hydrolysate 8644. Sacrez, R., et al.: Les hydrolysats de protéines en diététique infantile, Pediatrie **41**: 599-607, No. 5, 1952.

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8646. Tracy, W. H.: Psychotherapeutic gains with two contrasting cases in a children's institution, Delaware M. J. **24**: 218-223, Aug., 1952.

8647. Sontag, L. W., et al.: Dynamics of personality: resolution of infantile dependent need, Am. J. Orthopsychiat. **22**: 534-541, July, 1952.

Psychiatry, Techniques 8648. Arthur, H.: A comparison of the techniques employed in psychotherapy and psychoanalysis of children, Am. J. Orthopsychiat. **22**: 484-498, July, 1952.

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Purpura 8650. Meyers, M. C., et al.: The use of ACTH and cortisone in idiopathic thrombocytopenic purpura and idiopathic acquired hemolytic anemia, Ann. Int. Med. **37**: 352-361, Aug., 1952.

Pyloric Stenosis 8651. Schwartz, B., et al.: Congenital hypertrophic pyloric stenosis in a small premature infant, J. Pediat. **41**: 192-193, Aug., 1952.

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Reticulosis, Pulmonary 8654. Fontan, M., et al.: Réticulose pulmonaire du nourrisson à évolution maligne, Arch. franç. pédiat. **9**: 773-776, No. 7, 1952.

Rheumatic Diseases 8655. Kelley, V. C.: Corticotropin (ACTH) therapy of initial attacks of acute rheumatic fever in children, Am. J. Dis. Child. **84**: 151-164, Aug. 1952.

Rheumatoid Arthritis 8656. Kelly, M.: Chronic rheumatic (rheumatoid) monarthritis, M. J. Australia **2**: 79-83, July, 19, 1952.

Rickets 8657. Hövels, O., et al.: Untersuchungen über Wirksamkeit und Fehlerquellen der Rachitsprophylaxe im Säuglingsalter, Ztschr. Kinderh. **71**: 286-300, No. 3, 1952.

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Rubella 8658. Rutstein, D. D., et al.: Seasonal incidence of patent ductus arteriosus and maternal rubella, Am. J. Dis. Child. **84**: 199-213, Aug., 1952.

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School Health 8660. Simmons, R. L.: The role of the physician in the school health program, New Orleans M. & S. J. **104**: 574-578, Aug., 1952.

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Spleen 8665. King, H., & Shumacker, H. B., Jr.: Splenic studies, Ann. Surg. **136**: 239-242, Aug., 1952.

Statistics 8666. Nichols, J. B.: Statistics of births in the United States, Am. J. Obst. & Gynec. **64**: 376-381, Aug., 1952.

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Tetanus 8670. Wright, E. A., et al.: The site of action of the toxin in local tetanus, Lancet **2**: 316-319, Aug., 16, 1952.

Thrombophlebitis 8671. Thurel, R., et al.: Thrombophlébite de la veine de Galien chez un nourrisson hémorragies des noyaux gris centraux et de l'épiphyse, Arch. franç. pédiat. **9**: 746-747, No. 7, 1952.

8672. Zweymüller, E.: Phlegmasia caerulea dolens, Arch. Kinderh. **145**: 40-58, No. 1, 1952.

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Thrombophlebitis, Sinus 8674. Shaw, R. E.: Cavernous sinus thrombophlebitis: a review, Brit. J. Surg. **40**: 40-48, July, 1952.

Thumb-sucking 8675. Gandler, A. L.: Nature and implications of thumb-sucking, Arch. Pediat. **69**: 291-295, July, 1952.

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Toxoplasmosis 8677. Murphy, W. F., & Flannery, J. L.: Congenital toxoplasmosis occurring in identical twins, Am. J. Dis. Child. **84**: 223-226, Aug., 1952.

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Tryptic Activity 8679. O'Brien, D., & Powell, B. W.: Tryptic activity of stools in the newborn, Great Ormond Street J. No. 3: 33-35, June, 1952.

Tuberculoma, Cerebellar. See No. 8688.

Tuberculosis, BCG 8680. Wissler, H.: Zur Frage der Misserfolge bei BCG-Impfung, Schweiz. med. Wchnschr. **82**: 791-792, Aug., 2, 1952.

Tuberculosis 8681. Proske, G.: Bemerkungen zur Conteben-behandlung im kindesalter, Arch. Kinderh. **145**: 27-39, No. 1, 1952.

8682. Bossert, O., et al.: Antibiotische und Chemotherapie der kindlichen Tuberkulose, Arch. Kinderh. **145**: 3-26, No. 1, 1952.

Tuberculosis, Hip 8683. Wood, F. G., & Wilkinson, M. C.: Tuberculosis of the hip joint in children, Brit. J. Radiol. **25**: 437-441, Aug., 1952.

Tuberculosis, Testing 8684. Mastromatteo, E.: Tuberculin patch testing survey of the rural school population in southwestern Manitoba, Canad. J. Pub. Health **43**: 296-299, July, 1952.

Tumors 8685. Symposium—Childhood malignancies, Texas J. Med. **48**: 557-571, Aug., 1952.

Tumor, Acoustic 8686. Mark, V. H., & Sweet, W. H. An unusual case of unilateral eighth nerve tumor, J. Neurosurg. **9**: 395-397, July, 1952.

Tumor, Adrenal 8687. Cefalu, V.: Adrenal neuroblastoma: blending of Pepper and Hutchinson types: case report, Ann. West. Med. & Surg. **6**: 572-574, Sept., 1952.

Tumor, Brain 8688. Lawson, D.: A case of cerebellar tuberculoma, Great Ormond Street J. No. 3: 49-55, June, 1952.

8689. Woolsey, R. E., et al.: Localization of intracranial neoplasms with radio-active diiodofluorescein, South. M. J. **45**: 789-793, Sept., 1952.

8690. Alajouanine, T., & Bertrand, I.: Dysplasie laminaire hypertrophique du cervelet associée a une malformation rénale avec gigantisme tissulaire, Rev. neurol. **86**: 289-299, No. 4, 1952.

Tumor, Colon 8691. Newns, G. H., & Donald, C.: A case of carcinoma of the colon, Great Ormond Street J. No. 3: 64-67, June, 1952.

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Ulcer, Gastric 8695. Busby, C. L., et al.: Development of bleeding gastric ulcer in a child with acute rheumatic fever treated with ACTH and cortisone, New Orleans M. & S. J. **104**: 583-585, Aug., 1952.

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Virus Diseases 8689. Beveridge, W. I. B.: Immunity to viruses, Lancet **2**: 299-309, Aug. 16, 1952.

Virus Pneumonia 8699. Garvelmann, W.: Untersuchungen zum vorkommen Angeblich virusbedingter Einschlusskörperchen im Rachenepithel, Ztschr. Kinderh. **71**: 268-272, No. 3, 1952.

Vitamins 8700. Urbach, C., et al.: Effect of individual vitamins A, C, E and carotene administered at high levels on their concentration in the blood, Exper. Med. & Surg. **10**: 7-20, No. 1, 1952.

Vitamin B_{12} 8701. Finberg, L., & Chow, B. F.: Lack of effect of supplementary vitamin B_{12} administered to premature infants, Am. J. Dis. Child. **84**: 165-167, Aug., 1952.

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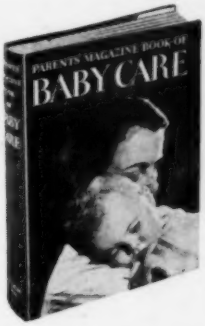

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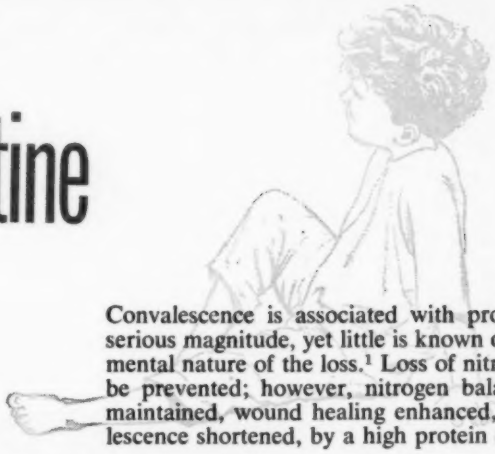

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1. Howard, J. E. Protein Metabolism During Convalescence After Trauma. Arch. Surg. 50:166, 1945.
2. Co Tui, Minutes of the Conference on Metabolism Aspects of Convalescence Including Bone and Wound Healing. Josiah Macy, Jr. Foundation, Fifth Meeting Oct. 8-9, p. 57, 1943.
3. Whipple, G. H. and Madden, S. C. Hemoglobin, Plasma Protein and Cell Protein: Their Interchange and Construction in Emergencies. Medicine 23:215, 1944.
4. Mulholland, J. H., Co Tui, Wright, A. M., Vinci, V., and Shafiroff, B. Protein Metabolism and Bed Sores. Am. Surg. 118:1015, 1943.

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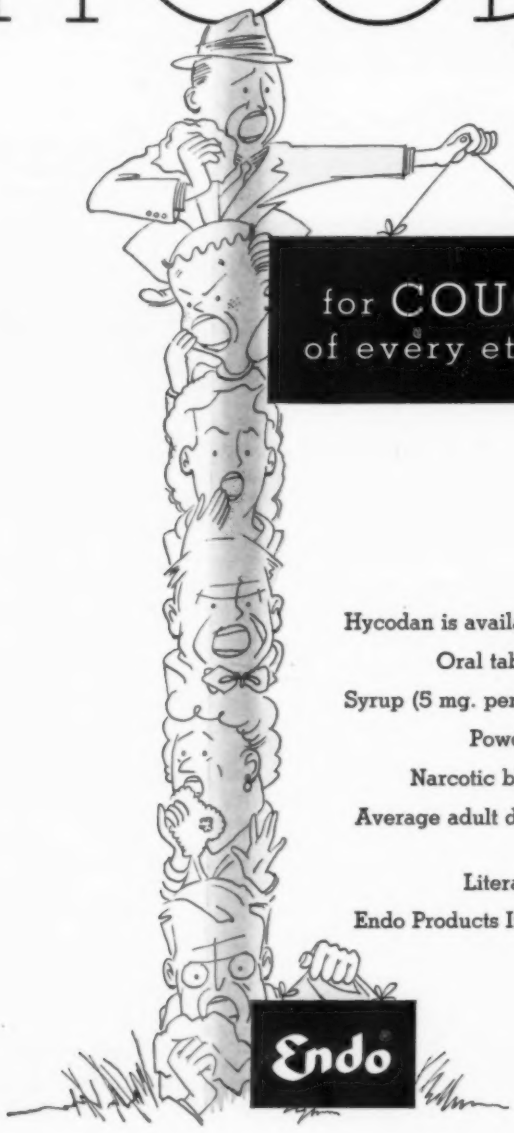

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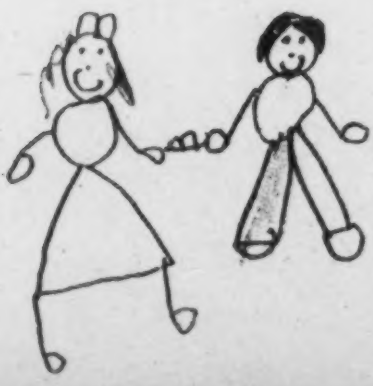

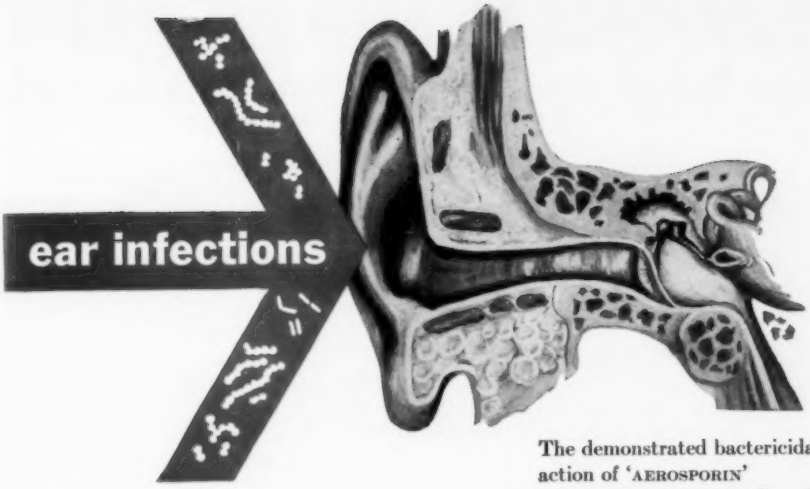

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References: 1. Salvin, S.B. and Lewis, M.L.: External Otitis with Additional Studies on the Genus Pseudomonas, J. Bact. *51*:495, 1946.

2. Hayes, M.B. and Hall, C.F.: The Management of Otogenic Infection, Tr. Am. Acad. Ophth. *51*:149, 1947.

3. Senturia, B.H.: Diffuse External Otitis: Its Pathology and Treatment, Tr. Am. Acad. Ophth. *54*:147, 1950.

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**Fries, J. H., Chiara, N. J., and Waldron, R. J.: Dehydrated Banana in the Dietetic Management of Diarrheas of Infancy, J. Pediat., 37:367, 1950.*

***Fries, J. H., and Glaser, I.: Studies on the Antigenicity of Banana, Raw and Dehydrated, J. Allergy, 21:169, 1950.*

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* Babies have *high-normal hemoglobin concentration when fed meat. Leverton, Clark, "Meat in the Diet of Young Infants," J.A.M.A., 134, 1215, (1947).* Also *Andelman, Gerald, Rambar, and Kagan, "Effects of Early Feeding of Strained Meat to Prematurely Born Infants," Pediatrics, 9, 485, (1952).*

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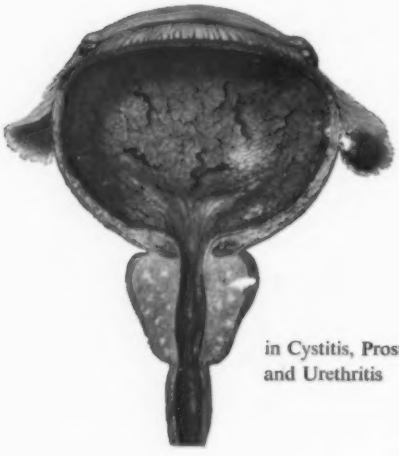

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1. Heimer, C. B., Grayzel, H. G. and Kramer, B.: Archives of Pediat. 68:382, 1951.
2. Behrman, H. T., Combes, F. C., Bobroff, A. and Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.

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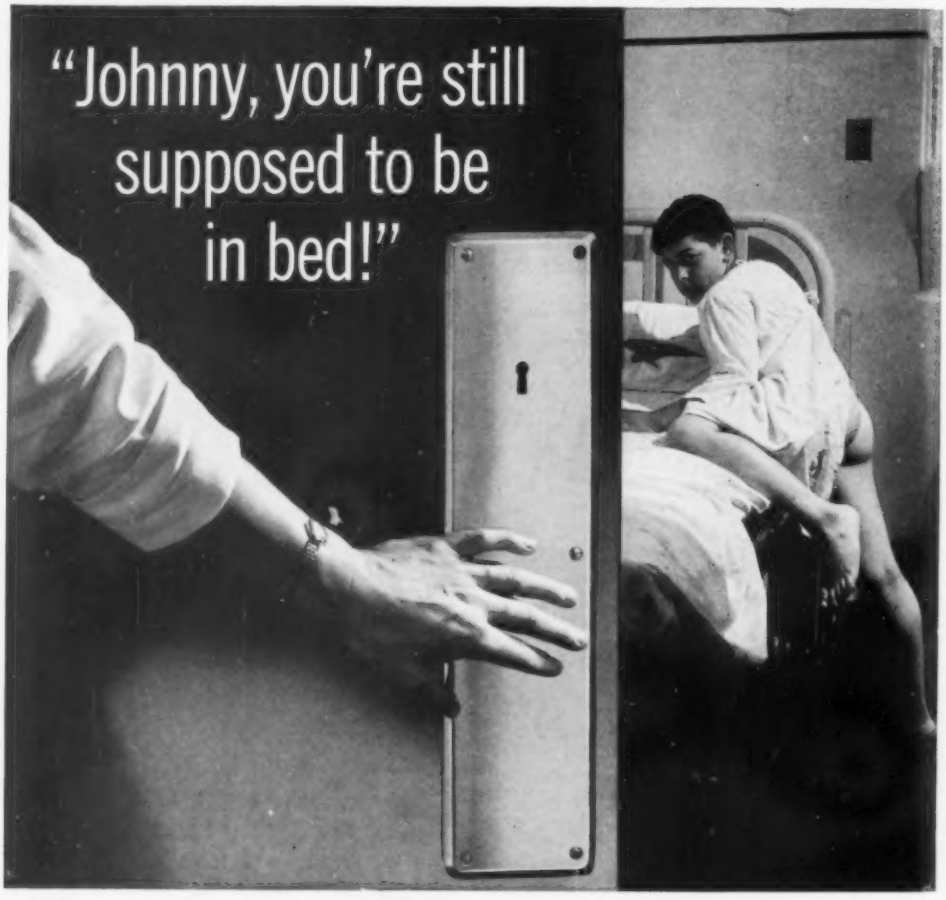

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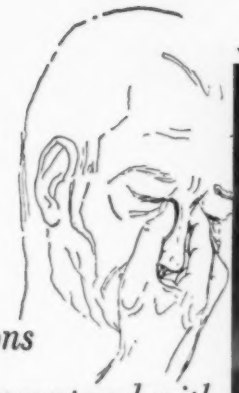

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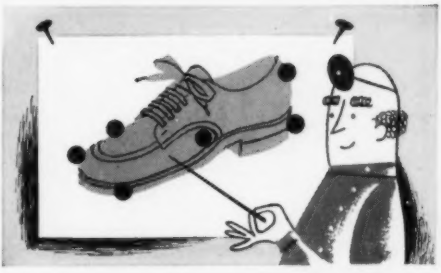

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1. Fisher, E. S. "Notes from The Office of the Chief Medical Examiner," Baltimore, Md., April, 1951.
2. Benson, E. A., et al.: "The Treatment of Ammonia Dermatitis with Diaparene," J. Ped. 34:1-49, Jan., 1949.
3. Niedelman, M. L., et al.: "Ammonia Dermatitis: Treatment with Diaparene Chloride Ointment," J. Ped. 37:5-762, Nov., 1950.

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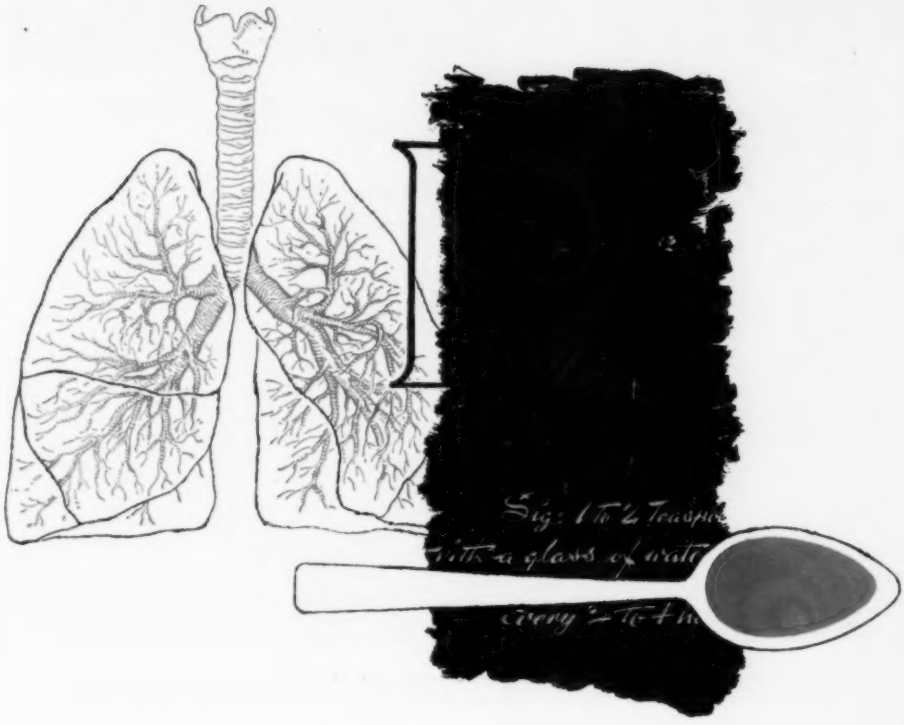

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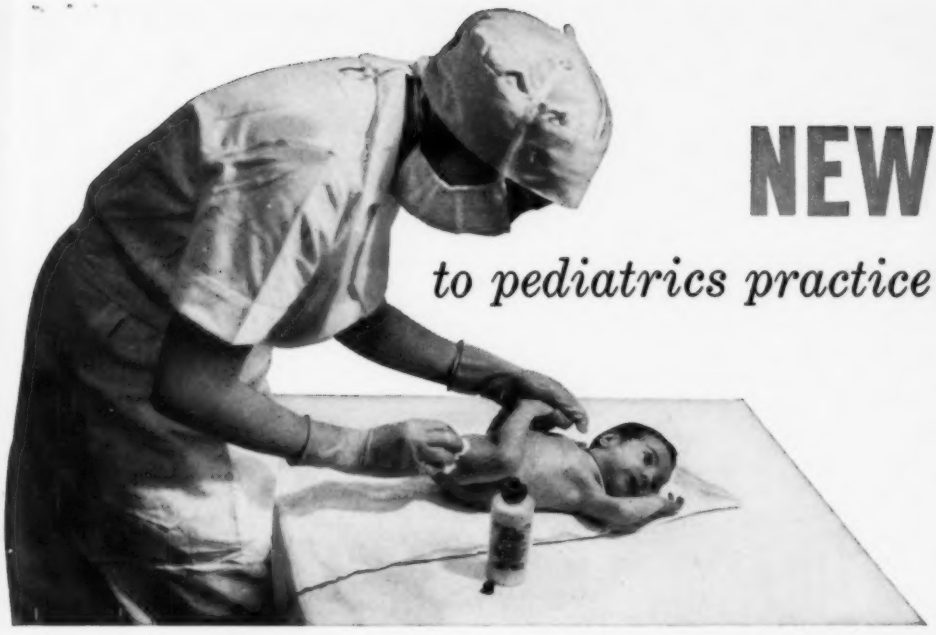

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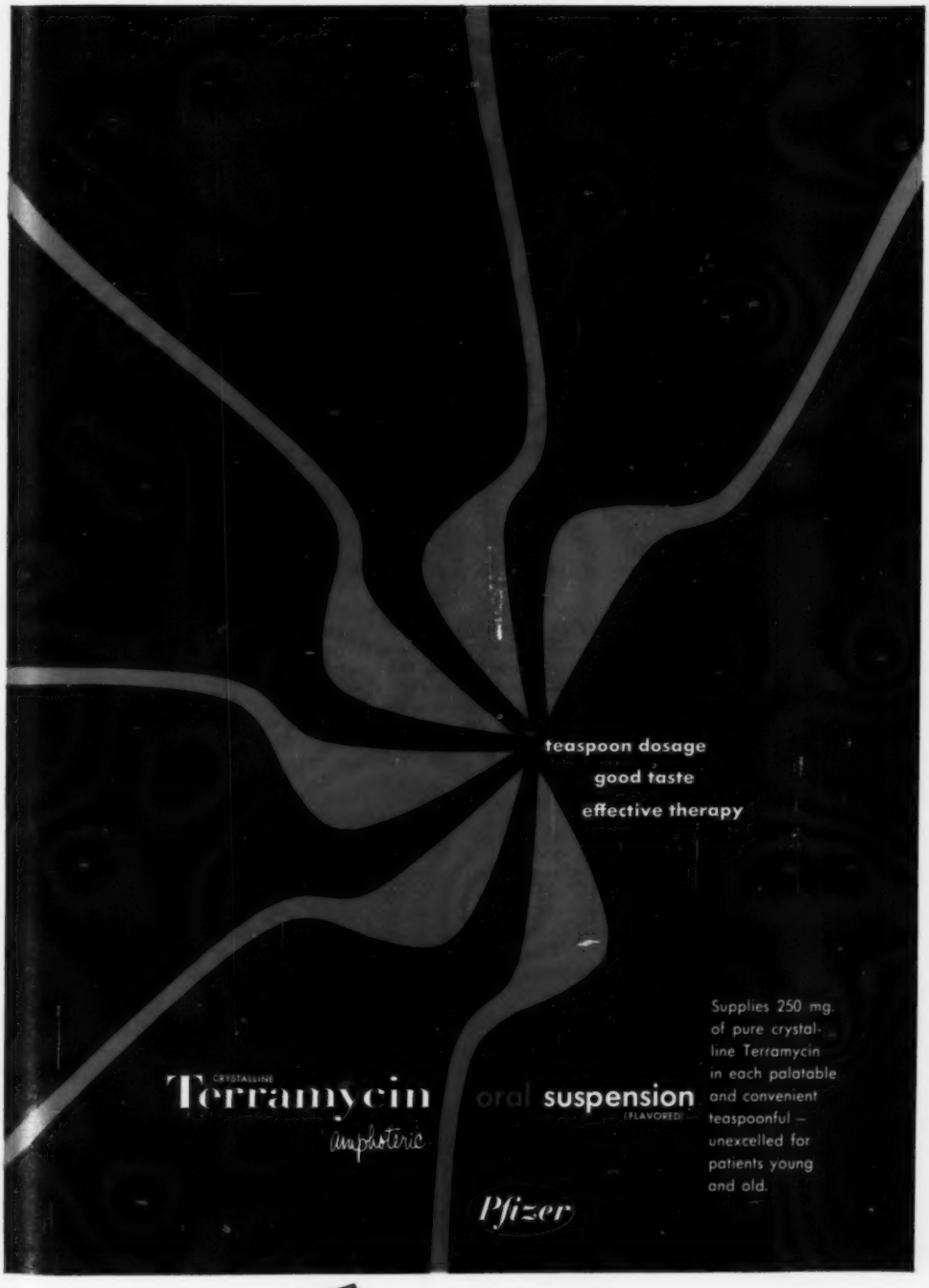

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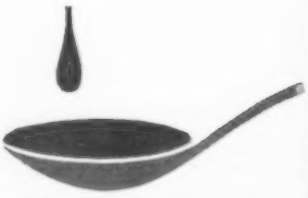

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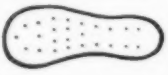

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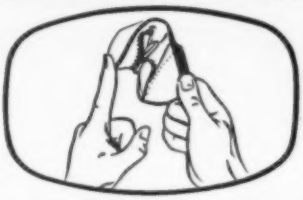

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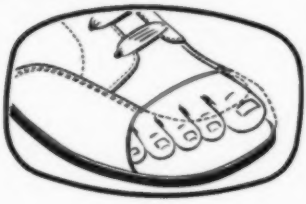

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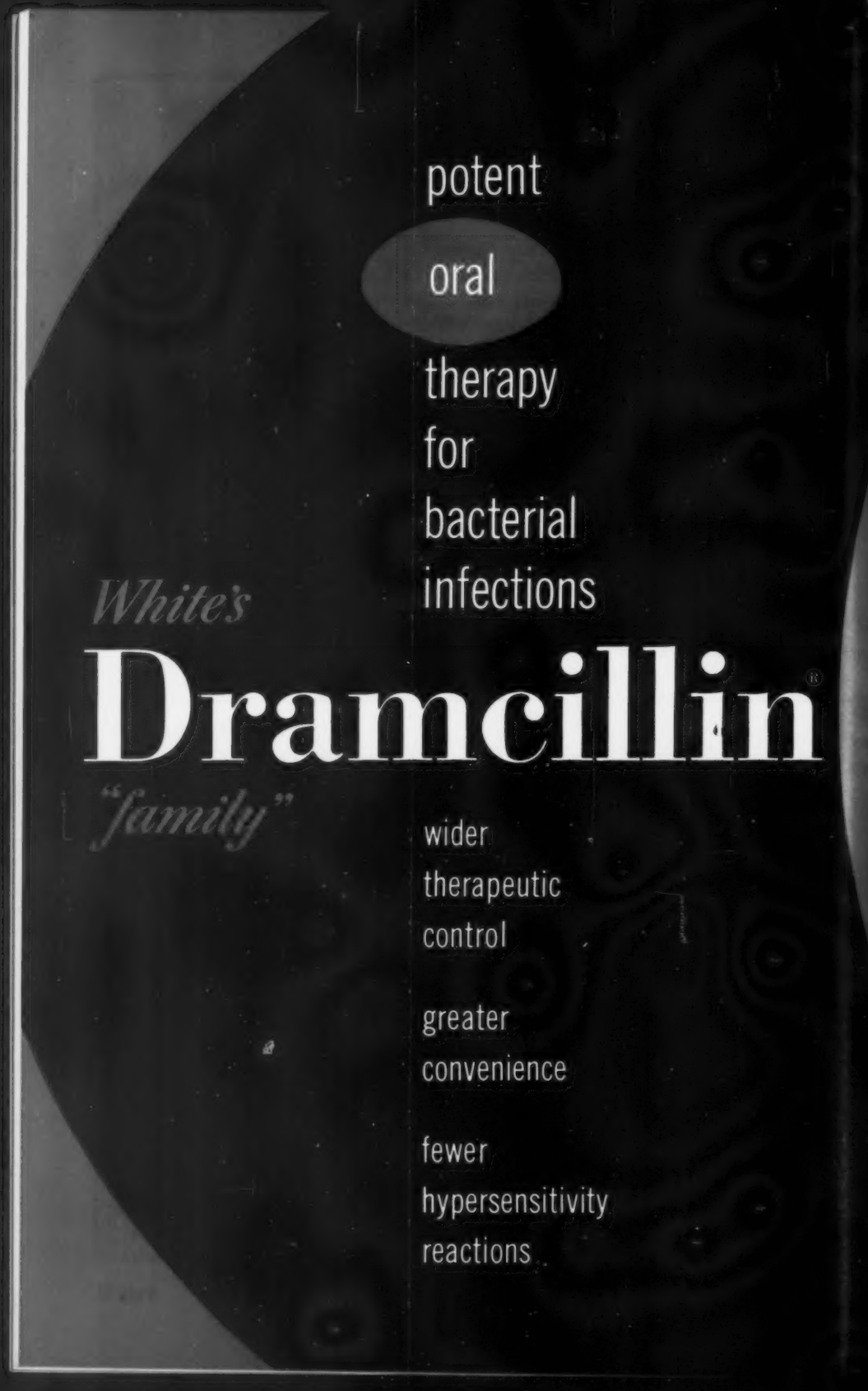
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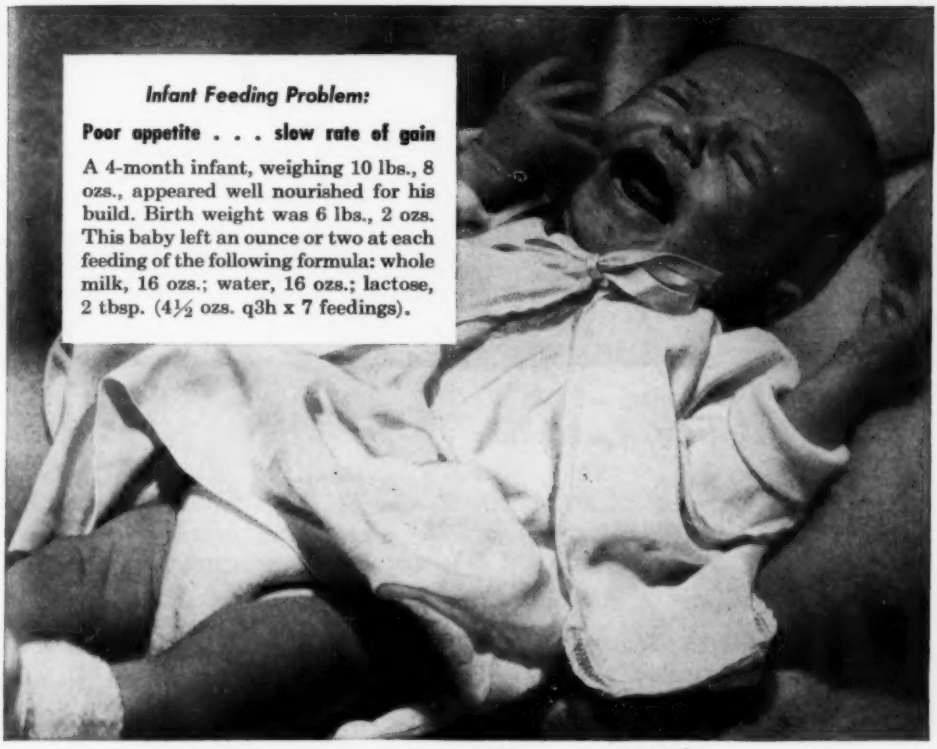

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